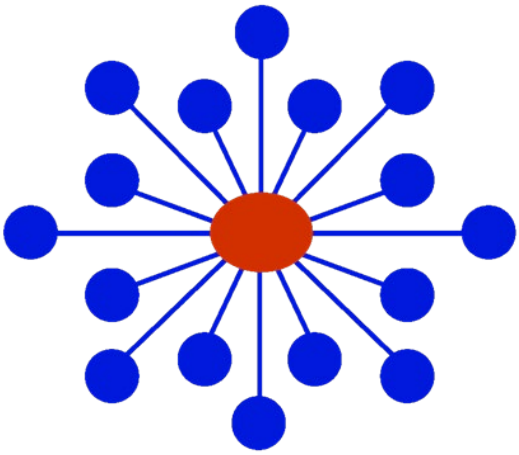

NIDA CTN Protocol 0067

Comparing Treatments for HIV-Infected Opioid Users in an Integrated Care Effectiveness Study (CHOICES) Scale-Up

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral
ASI-Lite	Addiction Severity-Index-Lite
AST	Aspartate Aminotransferase
BHIVES	Buprenorphine HIV Evaluation and Support Collaborative
BMI	Body Mass Index
BUP	Buprenorphine
BUP/NX	Buprenorphine Naloxone (Suboxone®)
CCC	Clinical Coordinating Center
CFIR	Consolidated Framework for Implementation Research
CCTN	Center for the Clinical Trials Network
CFR	Code of Federal Regulations
CHRT	Concise Health Risk Tracking
CI	Confidence Interval
CRF	Case Report Form
CTN	Clinical Trials Network
CTSA	Clinical and Translational Science Award
DEA	Drug Enforcement Agency
DSC	Data and Statistics Center
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federalwide Assurance

Abbreviation	Definition
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HCV	Hepatitis C Virus
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
IEC	Institutional Ethics Committee
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LFTs	Liver Function Tests
LI	Lead Investigator
MAT	Medication-Assisted Treatment
MAR	Missing at Random
Mg	Milligrams
MM	Medical Management
MMT	Methadone Maintenance Treatment
MNAR	Missing not at Random
MOP	Manual of Operating Procedures
NDA	New Drug Application
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NTX	Naltrexone
NX	Naloxone
OHRP	Office for Human Research Protections
OHSU	Oregon Health and Science University
ORT	Opioid Replacement Therapy

Abbreviation	Definition
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PLWHA	Persons Living with HIV/AIDS
PLG	Polylactide-co-glycolide
PWID	People Who Inject Drugs
QA	Quality Assurance
RAB	Risk Assessment Battery
RMVL	Repeated Measure of Viral Load
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SC	Subcutaneous
SOP	Standard Operating Procedures
TAU	Treatment as Usual
TLFB	Timeline Follow-Back
UDS	Urine Drug Screen
VACS	Veterans Aging Cohort Study
XR-NTX	Extended-Release Naltrexone (Vivitrol®)

2.0 STUDY SYNOPSIS AND SCHEMA

Substance use disorders are common in HIV-infected individuals [1-5]. Untreated substance use disorders are associated with increased HIV risk behaviors [6-8], decreased receipt of antiretroviral therapy (ART) [9], [7], [10-12], decreased ART adherence [7, 13-16], decreased HIV viral suppression [13, 17-20], greater HIV-related symptoms [21, 22], and higher hospitalization rates [23, 24]. Compared to other HIV risk groups, people who inject drugs (PWID) are less likely to engage in HIV care and achieve HIV viral suppression [13, 17, 25] or sustained viral suppression [26, 27].

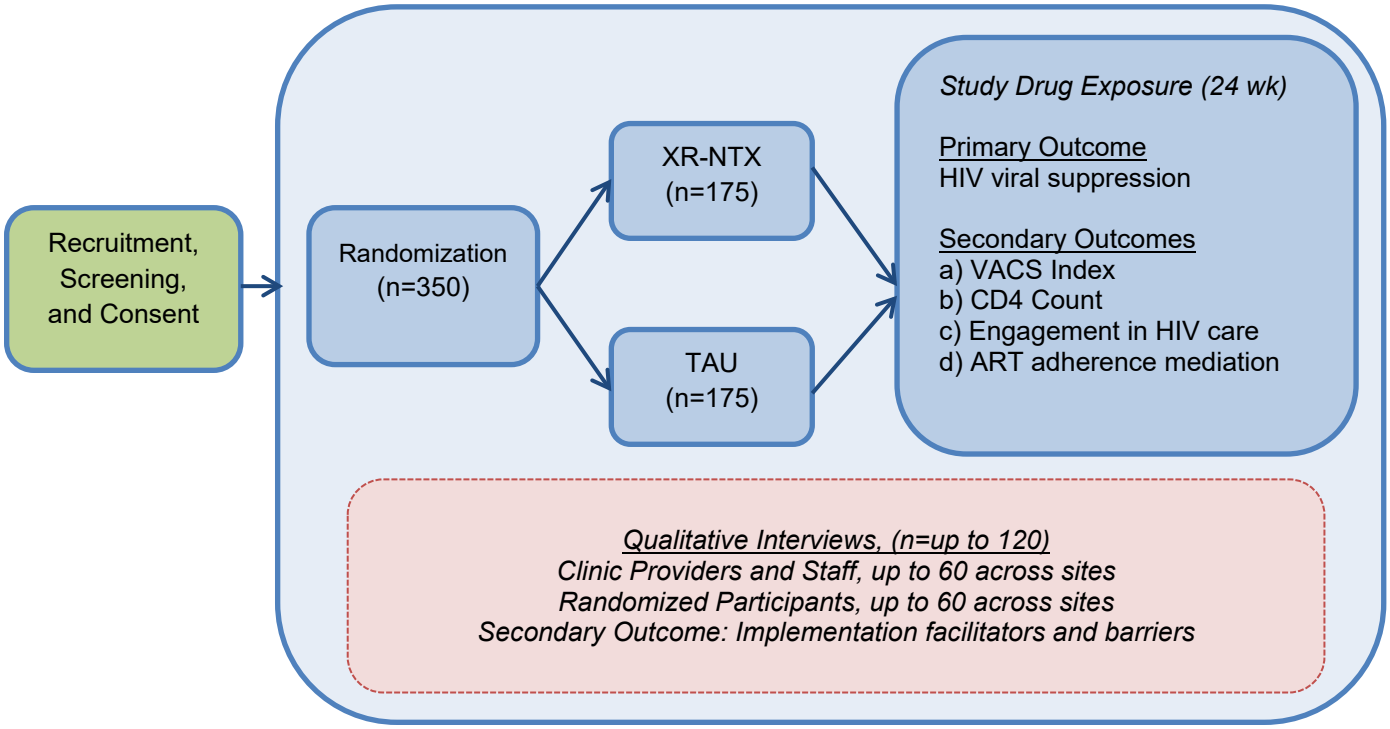
Treatment of substance use disorders can increase engagement in HIV care [28, 29]. Opioid replacement therapy (ORT) with methadone [30] and sublingual buprenorphine/naloxone (BUP/NX) [31] decreases HIV transmission risk behaviors and improves HIV outcomes, yet access to these medication-assisted therapies is limited and requires adherence to daily dosing.

HIV providers are well-positioned to integrate pharmacotherapy for substance use disorders into HIV treatment settings, but thus far only BUP/NX has been adopted in HIV practice. In the Buprenorphine-HIV Evaluation and Support (BHIVES) Collaborative (a demonstration of integrated care for HIV and opioid dependence), HIV-infected individuals with opioid dependence who received office-based BUP/NX from an HIV clinic provider decreased opioid use [32], increased ART use [29], experienced higher quality of HIV care [33] and reported better quality of life [34]. HIV treatment guidelines now recommend opioid agonist therapy as a key treatment strategy for engaging PWID in HIV treatment [35]. Retention on agonist therapy remains limited, however, due to daily dosing requirements, and some patients would prefer alternatives to agonist treatment.

Long-acting antagonist treatment may provide an alternative to daily agonist therapy for patients with opioid use disorder, though its ability to facilitate closing gaps in HIV treatment retention and outcomes is unknown. Extended-release naltrexone (XR-NTX), a deep muscle injection that lasts 28 days, eliminates the need for daily dosing. XR-NTX improves alcohol dependence treatment adherence and retention when integrated into primary care clinics [36, 37], but has not been tested in people living with HIV who are having difficulty engaging in HIV treatment. XR-NTX may also be preferred by some HIV-infected patients seeking a non-narcotic treatment option and/or once a month dosing.

The CTN-0055 CHOICES pilot study demonstrated the feasibility of extended-release naltrexone (XR-NTX) for treatment of opioid use disorder in HIV primary care at two HIV clinic pilot sites. The CTN-0067 CHOICES scale-up study builds on lessons learned from the pilot and uses the Consolidated Framework for Implementation Research to advance understanding of XR-NTX adoption in HIV primary care settings. CTN-0067 CHOICES scale-up study is conducted in no more than 8 HIV primary care clinics. It is an open-label, randomized, comparative effectiveness trial of office-based XR-NTX for 24 weeks (approximately 6 monthly injections) (n = 175) versus treatment as usual (TAU) (n = 175) in HIV-infected participants with untreated opioid use disorder and HIV RNA PCR > 200 copies/ml at baseline (**Figure 1**). The *primary outcome* is HIV viral suppression (HIV RNA PCR ≤ 200 copies/mL) at 24 weeks. *Secondary outcomes* include VACS Index, CD4 count, HIV care engagement, and ART adherence mediation. The trial will be powered as a non-inferiority trial because the overall goal of the research is to add to rather than supplant currently available effective treatments. An implementation assessement documents best practices. Each participant will be engaged in the overall study for 25 to 28 weeks, depending on the speed of screening and enrollment procedures.

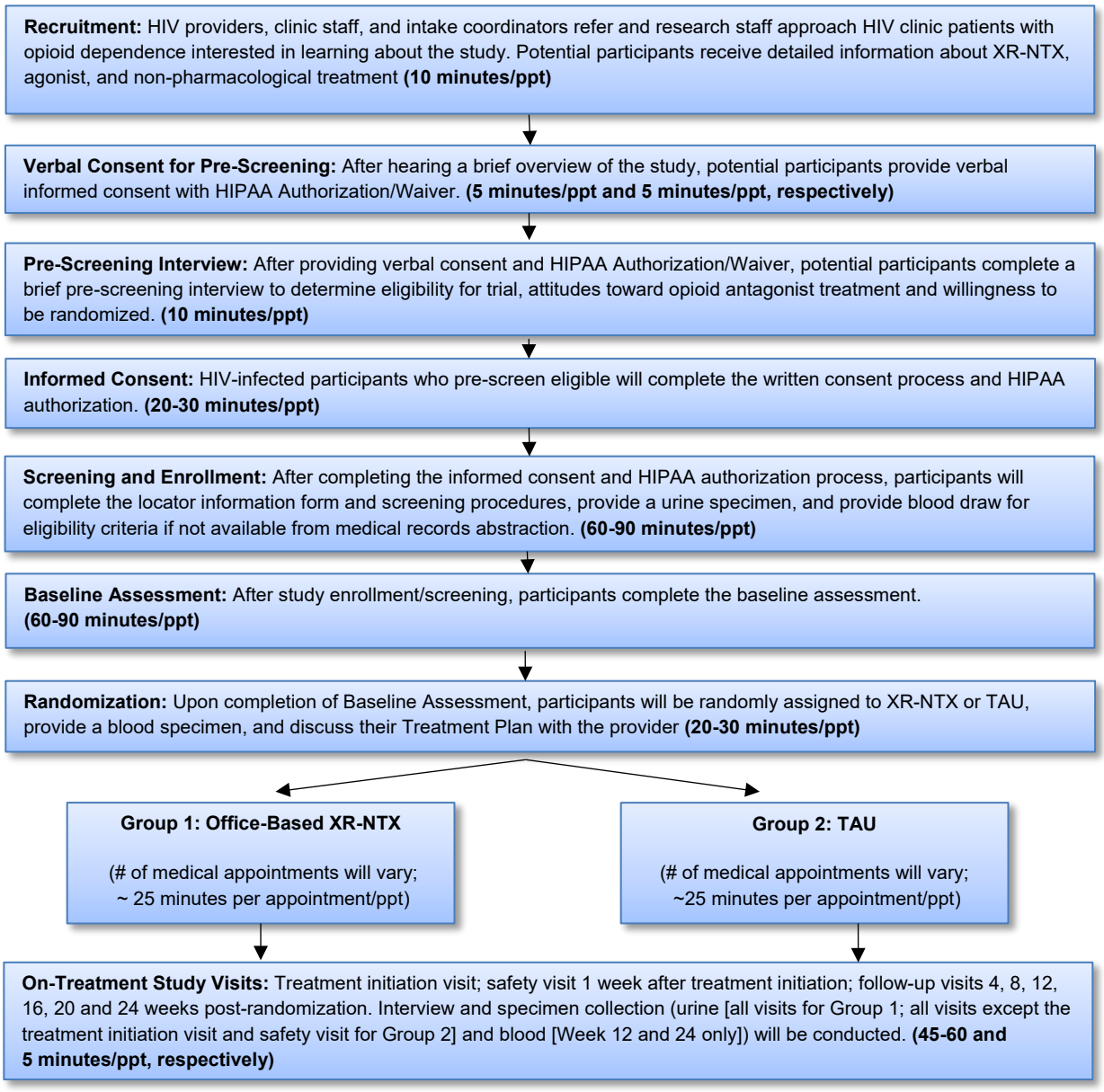
2.1 Figure 1. Study Schema



Specific Aim: The *specific aim* is to compare the effect of office-based extended-release naltrexone (XR-NTX) versus treatment as usual (TAU) on HIV viral suppression at 24 weeks from randomization for HIV-infected participants with untreated opioid use disorder and HIV RNA PCR > 200 copies/ml at baseline.

Secondary Specific Aims: Secondary aims compare the effectiveness of XR-NTX versus TAU in 1) other HIV outcomes (VACS Index, CD4 count), 2) engagement in HIV care (receipt of ART, ART adherence, retention in HIV care, HIV risk behaviors), 3) ART adherence as mediated by number of opioid use days at 24 weeks, and 4) qualitiative interviews with participants, providers, and staff to document the HIV primary care treatment environment and describe XR-NTX formative implementation strategies, challenges, and best practices.

3.0 STUDY FLOW CHART



4.0 INTRODUCTION

4.1 Background and Rationale

Opioid Use Disorders in People Living with HIV. Opioid use disorders are common in HIV-infected individuals [3, 38, 39]. Patients with opioid use disorder experience wide gaps in the HIV care cascade. Only 21% of HIV-infected individuals referred are established and retained in ongoing HIV care [25] and PWID are least likely to engage in HIV care and achieve HIV viral suppression compared to other HIV risk groups [13, 17, 25].

When untreated, opioid use disorder in people living with HIV is associated with decreased receipt of antiretroviral therapy (ART) [9, 40], decreased ART adherence [14], and decreased HIV viral suppression [13, 17-19]. Other adverse outcomes include decreased health-related quality of life [34], greater HIV-related symptoms, [21], higher hospitalization rates [23], and greater HIV disease progression and death [41]. Opioid use disorder is also associated with increased HIV risk behaviors [8].

Opioid Use Disorder Treatment and HIV Outcomes. Treatment of opioid use disorders with methadone or buprenorphine can improve engagement and retention in care, receipt of ART, ART adherence, and HIV viral suppression. The International Association of Providers of AIDS Care guidelines recommend scale-up of evidence-based medication-assisted treatments for substance use disorders for optimizing the HIV care continuum [42]. Over four decades of evidence demonstrate that methadone maintenance therapy (MMT) is both efficacious in clinical trials and effective in the community in promoting and sustaining abstinence and reducing risks associated with opioid use disorders [39, 43]. In a cohort of HIV-infected PWID in Vancouver, British Columbia, MMT was associated with greater ART adherence (AOR 1.52; 95% CI 1.16-2.00), HIV-1 RNA suppression (AOR 1.34; 95% CI 1.00-1.79), and CD4 cell count rise (AOR 1.58; 95% CI 1.26-1.99) over time [44].

The approval of buprenorphine for office-based treatment of opioid dependence expanded patient treatment options and access to addiction care. In a pilot trial (n=93) of clinic-based buprenorphine vs. referral for methadone maintenance, HIV-infected participants randomized to clinic-based buprenorphine treatment were more likely to engage in treatment for opioid dependence compared to those referred for methadone (74% vs. 41%, p<.001); however, ART receipt, HIV RNA and CD4 counts did not differ at 12 months [28]. In the Buprenorphine HIV Evaluation and Support Collaborative (BHIVES), HIV-infected individuals with opioid dependence who received clinic-based buprenorphine/naloxone (BUP/NX) from an HIV clinic provider decreased opioid use [32], experienced higher quality of HIV care [33] and reported better quality of life [34]. A majority (60%) of BHIVES participants were already on ART at baseline. Participants initiating clinic-based BUP/NX (N = 295) were significantly more likely to initiate or remain on ART and improve CD4 counts over time compared with baseline. Retention on BUP/NX for three or more quarters was associated with increased likelihood of initiating ART (β = 1.34 [95% CI 1.18, 1.53]) and achieving viral suppression (β = 1.25 [95% CI 1.10, 1.42]) among the 64 of 119 (54%) participants not on ART at baseline compared with the 55 participants not retained on buprenorphine [29].

Opioid agonist therapy with methadone [30] or sublingual BUP/NX [31] is associated with decreases in HIV risk behaviors. A meta-analysis of 12 studies assessing the impact of opioid substitution treatment on HIV transmission showed a 54% reduction in HIV infection among PWID [45].

Need for Expanded Opioid Treatment Options in HIV Clinics. Despite the availability of MMT in most communities and recent adoption of office-based buprenorphine in some HIV practices,

an expanded palette of treatment options for opioid use disorder in HIV clinics is greatly needed. Only a minority of HIV-infected patients with substance use disorders receive addiction treatment [3, 46]. For those who receive pharmacologic treatment for opioid use disorder, treatment success is often limited by the need for daily dosing adherence for both methadone and buprenorphine.

MMT is tightly regulated and requires provider or self-referral to federally certified treatment centers for management. Some patients may prefer a once monthly treatment that can be administered in a primary care setting. Furthermore, HIV-infected participants receiving antiretroviral therapy with efavirenz or certain protease inhibitors can experience clinically significant reductions in methadone levels [47-49] and increases in buprenorphine levels [50, 51] that complicate methadone and buprenorphine dosing and ART choice. HIV providers are well-positioned to integrate novel treatments for substance use disorders, such as XR-NTX, into outpatient HIV practice. For example, BHIVES demonstrated that HIV providers and their patients readily adopted use of office-based buprenorphine for treatment of opioid dependence [32].

Naltrexone Treatment of Opioid Use Disorder. Naltrexone (NTX), a full mu-opioid antagonist, has been FDA-approved for opioid pharmacotherapy since the 1980s. Though highly efficacious when taken as prescribed, oral daily dosing requirements limit its effectiveness due to lack of adherence. Consequently, it is rarely used as first-line treatment for opioid use disorders in the community [52, 53]. Two recent studies of XR-NTX: 1) Comer et al. [54], testing Depotrex®, Biotech Inc., in New York City and Philadelphia; and 2) Krupitsky et al. [55], testing Vivitrol®, Alkermes Inc., in Russia, support efficacy of XR-NTX compared to placebo injections. In October 2010, largely on the basis of the Russian trial and an earlier U.S. safety study (Alkermes ALK21-006 and ALK21-006EXT), the FDA approved Vivitrol® for the prevention of relapse to opioid dependence. Patients and providers now have a remarkable opportunity to choose between two pharmacologically distinct treatment approaches, XR-NTX and BUP/NX, each with established efficacy, to expand options for medication-assisted recovery.

Yet little is known about XR-NTX implementation in U.S. office-based settings, and the FDA's decision has been criticized insofar as (1) the FDA "accepted a single trial of injectable naltrexone in Russia, unpublished at the time, as primary evidence of efficacy," and (2) "the study did not adequately assess risk of post-treatment overdose" [56]. Because agonist therapy is prohibited in Russia, these authors question the use of these data to gain approval in the USA where methadone and buprenorphine are widely available. Regardless of the merit of these concerns, the data from the Russian placebo-controlled efficacy trial do not directly address the effectiveness, implementation issues, safety, and costs of XR-NTX in U.S. HIV-infected populations.

Naltrexone for Treatment of Comorbid Alcohol Use Disorder. The CTN-0055 CHOICES pilot study demonstrated that 16% of participants with opioid use disorder had comorbid alcohol use disorder. Oral naltrexone received FDA approval in 1994 for treatment of alcohol use disorders and systematic reviews support its efficacy compared to placebo [57-61]; however, its success is limited by suboptimal adherence to daily dosing requirements [62, 63]. XR-NTX, which lasts 28 days, has improved response rates in alcohol-dependent patients. In a 6-month, multicenter trial of XR-NTX for alcohol dependence, those randomized to receive 380mg XR-NTX experienced a 25% greater decrease in heavy drinking day event rate compared to placebo [64], improved quality of life [65], and decreased holiday drinking [66]. In a post-hoc analysis limited to those with higher severity alcohol dependence, XR-NTX reduced heavy drinking days by 37% and compared with a 27% reduction for placebo-treated participants' improved maintenance of abstinence [67]. Treatment responses were highest among participants with at least 4 days of voluntary alcohol abstinence prior to their first dose of XR-NTX [64, 68], and were rapid in onset, with significant reductions in alcohol use observed after only 2 days [69]. XR-NTX did not significantly increase counseling or support group participation [69].

An open-label implementation study evaluating XR-NTX treatment of alcohol dependence in primary settings demonstrated that integrating XR-NTX was feasible and associated with marked reductions in drinking days and heavy drinking days, and improved abstinence [36, 37]. Participants completed a median 38 weeks (range 16-72) of treatment, with a median 8 monthly injections (range 4-15).

Naltrexone in HIV-infected populations. The CHOICES study is the first to assess XR-NTX in an HIV-infected clinic-based population. Daily oral naltrexone has been safely used to treat opioid and alcohol use disorders in HIV-infected persons. Tetrault, et al. assessed changes in liver enzymes and HIV biomarkers in 114 HIV-infected U.S. veterans 365 days before, during, and 365 days after treatment with oral naltrexone [70]. Co-morbidities common among the participating veterans were: opioid dependence (32%), alcohol dependence (89%), and hepatitis C (53%). About half (52%) received antiretroviral therapy during naltrexone treatment. Participants were prescribed naltrexone for a median 49 days (interquartile range 30-83 days). Mean AST and ALT levels decreased during and after naltrexone treatment. Two of 114 participants (1.8%) experienced mild liver enzyme elevations during naltrexone treatment, less than 5-times the upper limit of normal, which resolved upon treatment discontinuation. Mean HIV RNA levels decreased after naltrexone treatment and mean CD4 count remained stable throughout. This study suggests the risk of hepatotoxicity is minimal in HIV-infected participants treated with naltrexone, and that there are no adverse immunologic or virologic effects of treatment.

XR-NTX safety in HIV-infected populations is further demonstrated in HIV-infected persons randomized to XR-NTX following release from prison, who experienced no change in hepatic enzymes compared to those receiving placebo [71]. HIV/HCV co-infection has no effect on XR-NTX hepatic safety [72].

Naltrexone has been associated with risk-taking behavior. When combined with behavioral therapies, naltrexone was associated with reduced use of benzodiazepines and injection of buprenorphine among opioid injecting people in the Republic of Georgia [73].

Naltrexone and potential for ART Drug-Drug Interactions. Naltrexone is metabolized through both hepatic glucuronidation and minor extra-hepatic metabolism. When taken orally, it undergoes extensive first-pass metabolism, with reduction of naltrexone to the active metabolite 6-beta-naltrexol by dihydrodiol dehydrogenase. 6-beta-naltrexol levels are much lower with injectable extended-release naltrexone [74-76]. Elimination of conjugated naltrexone and 6-beta-naltrexol is through renal excretion. Naltrexone has no effect on Cytochrome P450 metabolism. It is thus unlikely to have clinically significant drug-drug interactions with antiretroviral medications. There are theoretical interactions possible between naltrexone and antiretrovirals that undergo glucuronidation, such as raltegravir (a substrate of UDP-glucuronosyltransferase [UGT] 1A1) and zidovudine (a substrate of UGT 2B7). A pharmacokinetic study of oral zidovudine administered to 15 participants taking oral naltrexone revealed no change in area under the curve (AUC) for zidovudine compared to controls [77].

Potential Effect of Naltrexone on HIV Viral Suppression and Immune Function. In the observational study of HIV-infected veterans receiving oral naltrexone for opioid or alcohol dependence, mean HIV RNA levels decreased after naltrexone treatment and mean CD4 count remained stable throughout [70]. While the majority of decline in HIV viral load is likely due to increased receipt of or adherence to antiretroviral therapy, declines persisted even after adjusting for antiretroviral use in this study. This raises the possibility that naltrexone may have direct effects on HIV-1 viral activity. CD4+ lymphocytes express μ, κ, and delta opiate receptors that interact with opioid antagonists [78, 79]. *In vitro* studies suggest that naltrexone inhibits alcohol-mediated HIV entry and replication in T-lymphocytes [80]. Gekker, et al. demonstrated naltrexone potentiates antiretroviral activity of zidovudine and indinavir in HIV-1 infected CD4 cell cultures

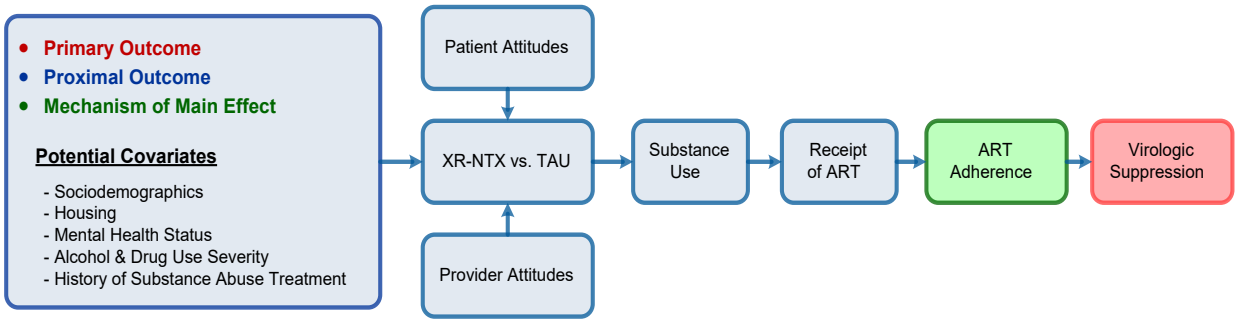
[81] and hypothesized potential synergism between naltrexone and antiretrovirals for reducing viral load.

Furthermore, naltrexone has non-opioid receptor activity that may have beneficial effects for HIV-infected participants. Toll-like receptors (TLR), a class of cell surface proteins that modulate innate immune responses, are expressed in many cells important to HIV pathogenesis and activated by opioid ligands. For example, activation of TLR 4 and TLR 8 by morphine in microglial cell cultures promotes inflammatory cytokine production and release of neurotoxic substances that may contribute to HIV-associated neural deficits when exposed to a bacterial challenge [82]. Morphine and bacterial challenge in microglia cultures from TLR4/TLR8 knock-out mice showed no increase in inflammatory cytokines or neurotoxins. Blocking these receptors with opioid antagonists suggests they may be important modulators of pain perception [83]. Naloxone and naltrexone are TLR 4 receptor antagonists that alleviate rat models of acute and chronic neuropathic pain [83] and reverse pain responses in microglial cell cultures [84]. Little is known about the effect of opioid antagonism on immune function, but CD4 cells express several TLRs and TLR activation appears to suppress innate immune responses that promote chronic viral infection with HIV [85] and HSV-2 [86], *in vitro*. The *in vivo* effect of TLR blockade with opioid antagonists on immune function and HIV viral activity is unknown. The CTN-0067 CHOICES study provides an opportunity to investigate novel direct effects of chronic opioid blockade on immune function and HIV viral suppression in a clinical population of HIV-infected participants.

Conceptual Model. Substance use disorders impair patient engagement and retention in HIV care, contributing to gaps in the HIV care cascade and suboptimal HIV viral suppression [87, 88]. The CHOICES study seeks to compare office-based XR-NTX vs. TAU for treating opioid use disorder in HIV-infected participants to improve engagement and retention in HIV treatment required for HIV viral suppression. Patient and provider attitudes assessed in the pilot study influence adoption of new treatment modalities [89]. The Consolidated Framework for Implementation Research (CFIR) suggests that patient, provider, and organizational attributes are key inputs to adoption of new evidence-based technologies in healthcare settings [90]. A CFIR analysis of the adoption of XR-NTX identified features of the technology (e.g., complicated ordering process, cold shipping requirements, preparation requirements, and cost), environmental issues (e.g., patient needs, health plan policies and reimbursements), practice setting concerns (e.g., changes in workflow, program culture, and communication requirements), and clinician characteristics (e.g., attitudes and self-efficacy) as potential barriers to routine use of the medication in routine practice [91].

CTN-0067 CHOICES Scale-up study compares the effectiveness of office-based XR-NTX versus TAU in achieving virologic suppression and decreasing opioid use. Virologic suppression reduces HIV associated morbidity, prolongs survival, restores and preserves immunologic function and decreases HIV transmission [92]. As shown in the conceptual model (**Figure 2**), HIV viral suppression is achieved through decreased use of opioids, which improves engagement in HIV care, receipt of ART, and ART adherence. Most HIV-infected patients with opioid use disorder who begin ART should be able to achieve virologic suppression if they continue in HIV care and adhere to ART [14, 93]. In this model, treatment of opioid use disorder is hypothesized as an important mediator of HIV viral suppression. HIV-infected participants with a history of substance use treatment are more likely to use HIV primary care and receive ART [94], [95]. The model also includes other covariates that may be related to engagement in HIV primary care or substance use treatment. Patient participant and provider qualitative interviews collected in parallel with outcome data enhance understanding of intervention characteristics with other CFIR domains, including the outer setting, inner setting, characteristics of the individuals involved, and the process of implementing XR-NTX in HIV clinic settings [90].

4.1.1 Figure 2. Conceptual Model



4.2 Naltrexone (NTX) and Extended-Release Naltrexone (XR-NTX)

NTX is a potent opioid antagonist with high affinity for the mu-opioid receptor. In the U.S., it is approved for use in treating opioid dependence and alcohol dependence. It is highly efficacious in preventing relapse to opioid dependence provided that it is taken as prescribed, but adherence with oral naltrexone is problematic and leads to extremely high dropout rates, with the occasional exception of treatment in criminal justice and other settings where relapse may be linked to severe adverse consequences [96-98]. This has led to intensive efforts – including NIDA- and NIAAA-funded grants to small businesses – to develop long-acting naltrexone preparations that can be administered as an injection or placed as an implant once per month or less frequently [99, 100].

XR-NTX (Vivitrol®, NTX-containing polylactide-co-glycolide [PLG] biodegradable sterile microspheres suspended in a diluent) is delivered by monthly injection into the muscles of the upper outer quadrant of the buttock. Each vial of microspheres contains 380 mg NTX which are suspended by adding a diluent that comes with the product and shaking for about a minute prior to injection of the full (less dead-space) content of the vial. Plasma concentrations of NTX and 6-beta-naltrexol (its main active metabolite) after a single XR-NTX injection are detectable for at least 30 days. Consistent with this, in human laboratory studies with Vivitrol® and Depotrex®, an essentially complete blockade of opioid agonist effects is seen for 30 days [101, 102]. To maintain blockade beyond 30 days, XR-NTX must be re-administered. Long-term use of NTX and XR-NTX is not associated with tolerance, dependence, addiction or withdrawal on discontinuation. NTX and XR-NTX will, however, precipitate withdrawal in individuals physiologically dependent on opioids and decrease opioid tolerance.

As a consequence of its extended duration of action and assured treatment adherence, XR- NTX may dramatically and favorably alter the limited effectiveness profile associated with orally administered NTX. By ensuring 30-day medication adherence with a single injection, and thereby establishing a ~30 day mu-opioid antagonist blockade, the likelihood of an individual re-establishing opioid dependence during this period is very low. Two clinical trials support efficacy for XR-NTX preparations compared to placebo injections [54, 55].

The 2006 Comer et al. study [54] was a proof-of-concept, 2-month randomized, placebo-controlled trial with a subcutaneously administered product (Depotrex®, Biotek Inc.), and showed that long-acting injectable naltrexone in conjunction with outpatient counseling produced superior treatment retention to placebo, providing evidence of the feasibility, efficacy, and tolerability of long-lasting antagonist treatments for opioid dependence.

The Krupitsky et al. study [55] was conducted in 2008 and 2009 in 13 sites in Russia, and was sponsored by the manufacturer, Alkermes, Inc. Following inpatient detoxification, 250 opioid-dependent participants were randomized to XR-NTX or placebo, double-blind monthly injections,

for 6-months, during which all participants received outpatient counseling. The percent of opioid abstinent weeks, by weekly urine toxicology, was the primary outcome. A response profile analysis compared the cumulative percent of participants at each level of the outcome (percent opioid-free weeks) between the active XR- NTX and placebo conditions. The difference between the response profiles was significant ($p < .0002$), with the median participant on XR-NTX having 90% abstinent weeks compared to 35% abstinent weeks for the median participant on placebo. Total abstinence (100% opioid-free weeks) was reported in 45 (35.7%) participants in the XR-NTX group versus 28 (22.6%) participants in placebo group ($p < .03$). Retention in treatment for the full 6 months was 53% on XR-NTX, compared to 38% on placebo ($p < .02$). The 6-month retention rate in the 50% range is similar to that observed in clinical trials of buprenorphine [103]. Participants treated with XR-NTX showed an approximately 50% sustained reduction in craving compared to no change in craving in the placebo group ($p < .005$). XR-NTX was generally well tolerated. Data from this trial supported Alkermes' supplemental NDA for treatment of opioid dependence.

Prescribing and Safety: Details on XR-NTX prescribing, pharmacokinetics and pharmacodynamics, metabolism and elimination, safety and toxicity are in the XR-NTX package insert.

4.3 Treatment as Usual (TAU)

The current standard of care for treatment of opioid use disorders in HIV clinics is opioid agonist therapy. Recent HIV treatment guidelines recommend office-based BUP/NX or referral for methadone maintenance for HIV-infected patients with opioid use disorders [35, 104]. Through the efforts of the Health Resources and Service Administration (HRSA)-funded Buprenorphine and HIV Evaluation Study (BHIVES) and Substance Abuse and Mental Health Services Administration (SAMHSA)-funded Physician Support Service for Buprenorphine, on-site treatment with office-based buprenorphine is increasingly being offered in HIV clinics. A recent HRSA HIV/AIDS Bureau monograph promotes adoption of office-based buprenorphine in HIV primary care [105]; see Section 4.1 for evidence of effectiveness of methadone and buprenorphine. Office-based BUP/NX, together with referral for methadone maintenance therapy, is now the standard of care for treatment of opioid use disorders in many U.S. HIV clinics [104].

Many HIV clinics in the U.S., including those associated with NIDA CTN nodes, receive Ryan White Care Act funding to provide ancillary services for under-insured and uninsured Persons Living with HIV/AIDS (PLWHA). These services typically include on-site case managers, social workers, and substance use counselors who provide critical treatment, referral, and support services for HIV-infected patients with substance use disorders. The site selection process will include a thorough review of existing treatment services.

PRELIMINARY DATA: CTN-0055 CHOICES Pilot: The CTN-0055 CHOICES pilot study tested patient and provider acceptability and feasibility of XR-NTX versus TAU for treatment of opioid and/or alcohol use disorder at two HIV clinic pilot sites (St. Paul's Hospital, Vancouver, B.C. and Core Center, Chicago, IL). Participants were enrolled without regard to baseline HIV viral suppression and opioid and/or alcohol use. The study was designed to continue until 50 participants were enrolled or 12 months elapsed, whichever came first.

Pilot study primary outcomes focused on 5 feasibility primary outcomes, which support the feasibility of a multi-site scale-up trial to assess the effectiveness of XR-NTX in HIV practice:

1) ***Provider Acceptability.*** HIV provider acceptability of XR-NTX was high in a survey of 107 HIV providers – more than 90% reported willingness to refer patients to a clinical trial of XR-NTX [106].

2) ***Patient Acceptability.*** Patients were interested in XR-NTX treatment, as well. The study site in Vancouver, B.C. conducted a survey of 657 persons who inject opioids as part of their site selection application. About half (52%) of the survey participants expressed willingness to receive XR-NTX treatment for opioid use disorder. Daily heroin injection was associated with increased willingness to try XR-NTX (OR 1.53, 95% CI 1.02, 3.12) [107]. Prospective CTN-0055 CHOICES pilot study participants (n=112) were asked about their willingness to participate in a trial of XR-NTX during pre-screening. Ninety-eight percent of prospective participants interested in reducing opioid use (n=60) and 99% of those interested in reducing alcohol use (n=82) were definitely or maybe willing to consider enrolling in a clinical trial of XR-NTX.

3) ***Randomization Rate.*** The CTN-0055 CHOICES pilot study enrolled 51 HIV-infected patients receiving care at two pilot site HIV clinics (mean age 46 years, mean CD4 count 620; 43% women). The trial achieved 155% actual versus expected randomizations, reaching randomization targets 4 months ahead of schedule and enrolling 22 (43%) participants with opioid and 29 (57%) with alcohol as their primary use disorder. Sixteen percent of randomized participants met criteria for *both* opioid and alcohol use disorders. Overall, the pilot study enrolled a mean of 3 participants per month per site.

4) ***Treatment Initiation.*** The majority (68%) of participants assigned to XR-NTX initiated treatment. Five of 12 (42%) participants with any OUD assigned to XR-NTX initiated XR-NTX within 4 weeks of randomization. The CTN-0055 CHOICES pilot study randomized participants prior to detoxification and provides the first benchmark for XR-NTX treatment initiation in community-dwelling people with opioid use disorder. Both of the two clinical trials of XR-NTX for opioid use disorder that led to FDA approval required successful residential detoxification prior to randomization and did not report treatment initiation rates [54, 55]. The CTN-0067 scale-up trial seeks to increase the rate of treatment initiation for participants with OUD with a modified naltrexone induction protocol (Section 9.2.3.1).

5) ***Treatment Retention.*** Of those initiating XR-NTX treatment, 88% were retained on XR-NTX at 16 weeks. Five of 5 (100%) participants with OUD who initiated XR-NTX were retained on XR-NTX at 16 weeks and received all four doses. This exceeds rates reported in the two previously reported clinical trials of XR-NTX for opioid use disorder that observed 68% retention on XR-NTX at 8 weeks in a U.S.-based study [54] and 57.9% at 24 weeks in a study of Russian PWID [55].

The CTN-0055 CHOICES pilot study documents the feasibility of XR-NTX treatment for opioid and/or alcohol use disorder in HIV clinics, but was not powered to assess the effect of XR-NTX on secondary outcomes, including HIV viral suppression and substance use.

Secondary outcomes generated point estimates for a multi-site trial:

1) ***HIV Viral Suppression.*** Overall, 80% of participants had a suppressed viral load (HIV RNA PCR ≤ 200 copies/mL) at baseline, and 84% were suppressed at 16 weeks. Among those with OUD, HIV viral suppression improved from 67% to 80% for XR-NTX and 58% to 75% for TAU. Among those with AUD, HIV viral suppression changed from 92% to 82% for XR-NTX and 100% to 100% for TAU. The very high proportion of participants with HIV viral suppression at baseline, particularly among those with only alcohol use disorder, has implications for design of a multi-site non-inferiority trial. Inclusion of participants suppressed at baseline in the scale-up study potentially biases scale-up results toward the alternative (i.e., non-inferiority) hypothesis. In other contexts, non-inferiority trials that cannot distinguish effective from ineffective treatments are said to lack assay sensitivity, jeopardizing the validity of a non-inferior result [108]. Pilot participants with OUD had lower baseline rates of viral suppression and substantial room for improvement. We also anticipate lower baseline HIV viral suppression rates in a scale-up to HIV clinics throughout the U.S., where HIV suppression rates are lower for persons who inject drugs than those observed at the two pilot sites [27, 109, 110]. The CTN-0067 CHOICES scale-up multi-site study seeks to limit the potential for a baseline ceiling effect by excluding participants with only alcohol use disorder and including participants with a non-suppressed HIV viral load at baseline.

2) ***Substance Use Outcomes.*** Among participants with OUD, mean days of opioids use in past 30 days decreased from 19 to 10 for TAU (n=12) and from 18 to 13 for XR-NTX (n=10). Among those with AUD, mean days of drinking to intoxication in the past 30 days decreased from 18 to 7 for TAU (n=11) and 13 to 6 for XR-NTX (n=12).

4.4 Significance to the Field

Expanding HIV providers' armamentarium for treating opioid use disorders and improving viral suppression in HIV-infected patients advances the three major goals of the National HIV/AIDS Strategy for the United States, updated for 2020, including 1) reducing new HIV infections in communities where HIV is most concentrated, 2) increasing access to care and improving health outcomes for people living with HIV, and 3) reducing HIV-related disparities and health inequalities [111]. The primary driver of HIV transmission is HIV viral load. If XR-NTX is effective in increasing viral suppression, fewer new HIV infections will occur among the sexual and drug-using partners of opioid and alcohol dependent individuals [112-114]. The CHOICES scale-up study increases access to care by engaging HIV-infected participants with suboptimal viral suppression to initiate and adhere to ART, and improves health outcomes by increasing viral suppression with resultant improvements in health outcomes and decreased mortality. The CHOICES scale-up study reduces HIV-related disparities and health inequalities by seeking to engage opioid-dependent participants in HIV treatment — a vulnerable population with persistently suboptimal access to high quality HIV care and outcomes, compared with other HIV risk behavior groups. The CHOICES scale-up study also advances the science of opioid use disorders treatment by directly comparing antagonist therapy with TAU in a comparative effectiveness trial to assess the implementation of a novel therapy into HIV clinical practice.

CTN-0067 is well-aligned with <u>three</u> NIH Office of AIDS Research high priority areas for HIV research funding:

1) <u>Reducing Incidence of HIV: developing, testing, and implementing strategies to improve HIV testing and entry into prevention services.</u> Opioid use disorders are barriers to engagement and retention in HIV care, and consequently HIV-infected patients with

these comorbid disorders are less likely to achieve HIV viral suppression compared with those without. Recruitment strategies will emphasize linkage with local HIV testing outreach efforts affiliated with HIV clinics to encourage entry into HIV treatment of substance users who are newly diagnosed with HIV.

2) Next generation of therapies-implementation research to ensure initiation of treatment as soon as diagnosis has been made, retention and engagement in these services, and achievement and maintenance of optimal prevention and treatment responses. CHOICES scale-up study will provide data on the effect of treating substance abuse on the HIV continuum of care stages: linkage, engagement, retention, and viral suppression. Treatment of underlying opioid use disorders with XR-NTX is likely to increase engagement and retention in HIV care, with consequent HIV viral suppression — the primary outcome for CHOICES scale up. The data gathered by the implementation component of CHOICES scale-up study should facilitate widespread adoption of XR-NTX by HIV clinics following the completion and publication of the study results.

3) Research to reduce health disparities in the incidence of new HIV infections and treatment outcomes. *Seventy-three percent* of CHOICES pilot participants were of minority race ethnicity. Scale-up sites will be predominately located in cities with local HIV epidemics that disproportionately affect African-American and Hispanic populations. CTN-0067 CHOICES scale-up study intervention is designed to increase engagement in HIV care leading to ART treatment (a secondary outcome) and HIV viral suppression (the primary outcome) for a predominantly minority race-ethnicity study population. Study outcomes and implementation lessons-learned will directly inform efforts to close race-ethnicity gaps in HIV treatment.

5.0 OBJECTIVES

5.1 Primary Objectives

The overarching goal of the CHOICES scale-up study is to determine the effectiveness of HIV clinic-based XR-NTX therapy in achieving HIV viral suppression in HIV-infected patients with opioid use disorder. Specific measures of study objectives outcomes are defined in Section 8.0.

Specific Aim: Compare HIV viral suppression (HIV-1 RNA ≤ 200 copies/ml) among study participants randomized to XR-NTX versus TAU at 24 weeks from time of randomization.

5.2 Secondary Objectives

Secondary Specific Aims: Secondary aims compare the effectiveness of XR-NTX versus TAU in 1) other HIV outcomes (VACS Index, CD4 count), 2) engagement in HIV care (receipt of ART, ART adherence, retention in HIV care, HIV risk behaviors), and 3) ART adherence as mediated by number of opioid use days at 24 weeks. An additional secondary aim assesses barriers and faciliators of implementing XR-NTX for retaining patients in HIV primary care.

1) Secondary HIV Outcomes

a. Change in VACS Index at 24 weeks, compared with randomization.

b. Change in CD4 count at 24 weeks, compared with randomization.

2) Engagement in HIV Care:

a. Proportion of participants prescribed ART within 24 weeks following randomization.

b. Proportion of participants taking 100% of prescribed ART doses in the past month at 24 weeks for those prescribed ART at any point during the 24 week trial.

c. Retention in HIV Care: Proportion of participants with at least 1 HIV primary care visit in the past 12 weeks, measured at week 24.

d. HIV Risk Behaviors, as measured by the RAB at week 24.

e. Quality of life as measured by EQ-5D at week 24, compared to baseline.

3) ART Adherence Mediation Variables:

a. Number of days of opioid use since baseline, measured by Timeline Follow Back (TLFB) at 24 weeks.

b. Past 30 day opioid abstinence (by Addiction Severity Index (ASI)-lite self-report, Timeline Follow Back (TLFB) and urine drug screen (UDS) confirmation at 24 weeks.

4) Assess barriers and facilitators of XR-NTX implementation to improve retention in HIV primary care:

Qualitative interviews with participants, providers, and staff to document the HIV primary care treatment environment and describe XR-NTX formative implementation strategies, challenges, and best practices.

6.0 STUDY DESIGN

6.1 Overview of Protocol Study Design

The CHOICES scale-up (CTN-0067) study is designed to compare the effectiveness of HIV clinic-based XR-NTX versus TAU in engaging HIV-infected persons with opioid use disorder in care to improve HIV viral suppression. The CTN-0067 CHOICES scale-up study builds on lessons learned from the pilot and uses the Consolidated Framework for Implementation Research [90] to advance understanding of XR-NTX adoption.

HIV clinics will serve as primary care clinic settings for CTN-0067. Eligible study sites must a) provide HIV primary care, b) have a sufficient population of potential participants to achieve study enrollment goals, c) have providers willing to be trained in use of XR-NTX for management of opioid use disorder, d) have the capacity to prescribe ART to participants, regardless of CD4 count, e) offer on-site addiction counseling services as part of usual care, and f) offer access to opioid agonist treatment, either on-site or by referral.

The CTN-0067 CHOICES scale-up study will utilize no more than 8 HIV primary care clinics to conduct the trial. The study is an open-label, randomized, comparative effectiveness implementation trial of office-based XR-NTX for 24 weeks (approximately 6 monthly injections) (n = 175) versus TAU (n = 175) in HIV-infected participants with untreated opioid use disorder (**Figure 1**).

In the pilot, 60 (85%) of 71 pre-screened individuals who reported using opioids in the past year said they were interested in stopping opioid use. Of these, 59 (98%) were willing to enroll in a clinical trial of XR-NTX for treatment of OUD, and 24 (41%) of those willing to try XR-NTX were randomized. Thus, 24 (34%) of 71 pre-screened individuals with past year illicit opioid use were ultimately randomized. Nine (38%) of these had an unsuppressed HIV viral load at baseline. Assuming the same proportion of pre-screened as randomized opioid users will be unsuppressed at prescreening, enrolling 350 participants in the scale-up may require pre-screening of about 2,709 [350/(0.34*0.38)] patients with past year opioid use.

The trial will be powered as a non-inferiority trial since the overall goal of the research is to add to rather than to supplant currently available effective opioid agonist treatment options. The *primary outcome* is the proportion of participants who achieve HIV viral suppression (HIV-1 RNA ≤ 200 copies/ml), measured at 24 weeks. *Secondary outcomes* include 1) other HIV outcomes (VACS Index, CD4 count), 2) engagement in HIV care (receipt of ART, ART adherence, retention in HIV care, HIV risk behaviors), and 3) ART adherence as mediated by number of opioid use days at 24 weeks. A fourth secondary objective documents facilitators and barriers of implementing XR-NTX to improve retention in HIV primary care (**Figure 1**).

6.2 Study Duration and Visit Schedule

The CTN-0067 CHOICES scale-up study will target enrolling 350 participants over approximately 22 months at no more than 8 HIV clinic sites. Each participant will be engaged in the overall study for an expected duration of 25-28 weeks (**Figure 3**) as follows:

- Weeks 1-4: consent, screening, randomization.
- 24 weeks: Active treatment with study visits every 4 weeks.
- Week 24: A single follow-up visit at the end of active treatment.

6.3 Justification of 24 weeks active treatment and timing of ART initiation

Assessment of the primary outcome of HIV viral suppression requires a minimum of 6 months, given the high potency of currently available ART regimens. While longer follow-up periods are required to assess sustained viral suppression, nearly all people initiating ART can now achieve an HIV viral RNA ≤ 200 copies/mL within 6 months of ART initiation. Participants not already taking ART at study enrollment will be encouraged to begin ART as soon as possible following enrollment. The timing of XR-NTX initiation or ART initiation is up to the discretion of the HIV provider on the basis of the patient's clinical priorities. Finally, previous efficacy trials of XR-NTX for opioid use disorder [55] and alcohol use disorder [64] provided 24 weeks of XR-NTX.

6.4 Justifcation of Implementation Study Procedures

Overview. The HIV primary care treatment environment is likely to change during the course of the study, reflecting broader healthcare policy changes in society. Documenting the HIV primary care treatment environment and describing XR-NTX formative implementation strategies, challenges, and best practices is crucial both for interpreting study findings and advancing understanding of generalizability and sustainability in other settings. A mixed-methods implementation analysis of HIV providers, staff, administrators, and study participants enrolled in CTN-0067 assesses barriers and facilitators to the use of XR-NTX in participating HIV clinics. Results inform policy-making for dissemination of clinic-based XR-NTX to other settings.

Qualitative Interview Justification. Qualitative interviews provide critical detail for enhanced understanding of the findings from the comparative effectiveness trial (Secondary Aim). Using the Taxonomy of Mixed Method Designs [115-117], our design has a QUAN + qual structure with simultaneous data collection and emphasis/weight placed on the quantitative (comparative effectiveness trial) efforts. Recurrent themes extracted from key informant interviews document provider, organizational, and participant experiences over time to examine these findings in parallel with staff surveys and study participant outcomes data (i.e., HIV viral suppression). This approach is consistent with Type I hybrid implementation study designs recommended for comparative effectiveness trials [118]. HIV clinic characteristics and provider attitudes (inner setting), as well as detail about the use of XR-NTX (intervention characteristics), and community awareness, linkage across service settings, and policy support (outer setting) help identify the full range of complex variables associated with implementation of clinic-based XR-NTX. This approach represents an innovative strategy to integrate available quantitative study results (Secondary Aim) to examine the provider, patient, organizational, and policy-level changes that influence the uptake of XR-NTX in HIV clinics. Corresponding with the CFIR, we identify individual, organizational and contextual characteristics that influence uptake of XR-NTX. We will particularly explore barriers to XR-NTX adoption identified in substance abuse treatment center setting using a CFIR framework, such as cost, complexity of prescribing, health plan policies, and reluctance to change [91]. Mixed-methods including QUAN + qual data are well suited for studying implementation of clinic-based XR-NTX and assessing the influence of individual and organizational characteristics on utilization.

Data Collection and Management. Lead Node investigators will conduct audio-recorded key informant interviews with HIV clinic providers, staff and administrators (up to 60 total across sites) over the study period. A convenience sample of CTN-0067 study participants assigned to XR-NTX (up to 60 total across sites) will be approached by site research staff and consented for participation in qualitative interviews. Interview guides use the CFIR framework to probe participant perceptions of the characteristics of XR-NTX and TAU (e.g., intervention quality, advantage, adaptability), outer setting (e.g., resources, social support, social interactions, external policies and incentives), inner setting (e.g., clinic organization, networks and

communication, practice culture, and implementation climate), provider characteristics (e.g., self-efficacy for XR-NTX treatment) and the implementation process (e.g., engaging, executing, evaluating) [90, 119]. Not all questions will be asked of all informants.

Audio-recorded interviews will be professionally transcribed, reviewed and summarized. Transcriptions will be password protected, stored on a secure network and uploaded into qualitative analysis software (Atlas.ti™) which organizes data and facilitates coding and thematic analysis.

Qualitative data will be supplemented with a brief survey of participating sites (*n* = no more than 8), completed prior to study initiation, to document local treatment environment (e.g., availability of clinic-based buprenorphine, state Medicaid support for medication-assisted treatment, amount of Ryan White Care Act funding, community referral resources, etc.).

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Individuals participating in the clinical trial must:

1) Be at least 18 years old.

2) Be willing and able to provide written informed consent and HIPAA Authorization (if applicable) for medical record abstraction.

3) Meet DSM-5 criteria for moderate or severe opioid use disorder.

4) Be willing to be randomized to antagonist-based therapy or TAU.

5) Have an HIV viral RNA count > 200 copies/ml. HIV viral RNA may be drawn with screening blood draw or abstracted from medical records if drawn in the 90 days prior to the date of consent.

6) Be willing to establish ongoing HIV care at the site if not already receiving ongoing care.

7) If female, be willing to take at least one evidence-based measure to avoid becoming pregnant.

7.2 Exclusion Criteria

Participants will be excluded if they:

1) Have a severe medical, psychiatric or substance use disorder that, in the opinion of the study physician, would make study participation hazardous to the participant, compromise study findings, or prevent the participant from completing the study due to imminent risk of death. Hospitalized patients who do not meet these conditions remain eligible for participation.

Examples include:

a. Acute life-threatening medical illness (e.g., uncompensated heart failure, end-stage liver disease, acute hepatitis or moderate to severe renal impairment) as assessed by medical history, review of systems, physical exam and/or laboratory assessments;

b. Severe, inadequately-treated mental health disorder in need of immediate treatment (e.g., active psychosis, uncontrolled manic-depressive illness) as assessed by history and/or clinical interview;

c. Suicidal or homicidal ideation requiring immediate attention.

2) Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) liver enzymes greater than 5 times upper limit of normal on screening phlebotomy. Results from tests conducted within the past 30 days from date of consent may be abstracted from medical records.

3) Have INR > 1.5 or platelet count <100k. Results from tests conducted within the past 30 days from date of consent may be abstracted from medical records.

4) Have known allergy or sensitivity to naloxone, naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the Vivitrol® diluents.

5) Anticipate undergoing surgery during study participation.

6) Have chronic pain requiring ongoing pain management with opioid analgesics.

7) If female, currently (at time of consent) pregnant or breastfeeding or planning on conceiving in the coming months.

8) Body habitus that, in the judgment of the study physician, precludes safe intramuscular injection of XR-NTX (e.g., excess fat tissue over the buttocks).

9) Received methadone or buprenorphine maintenance therapy for treatment of opioid use disorder in the 4 weeks prior to consent (medically supervised withdrawal therapy is allowed).

10) Received ongoing XR-NTX injections as maintenance therapy for opioid or alcohol use disorder in the 4 weeks prior to consent (does not exclude individuals leaving incarceration with a single injection and no specific follow up).

11) Have taken an investigational drug in another study within 30 days of study consent.

12) Are currently in jail, prison or any overnight facility as required by court of law or have pending legal action that could prevent participation in study activities.

7.3 Recruitment

HIV-Infected Participant Recruitment:

Study participants will be recruited from participating HIV outpatient clinics. HIV clinics likely to participate in CTN-0067 typically serve as patient-centered medical homes for HIV-infected participants, offering a broad array of on-site case management, social work, and counseling support services to engage and retain patients in care. All members of the HIV clinic care team will be educated regarding the study and asked to refer potential participants who are interested in learning more about the study to clinic research staff for screening. The site PI will either be an attending HIV provider in the HIV clinic or have strong relationships with HIV providers, so we anticipate excellent cooperation in approaching potential participants. Because the study seeks to improve engagement in HIV care, the HIV clinic care team and research staff will interact with community and hospital-based outreach services to identify and engage potential participants who are not currently engaged in HIV care. Outreach to and screening of hospitalized patients is encouraged, since they represent an enriched population of people with untreated HIV and opioid use disorder. If a participant is interested in learning more about the study, a study staff member will meet with the participant to discuss the study. Potential participants will be briefly instructed regarding opioid agonist and antagonist therapy and complete a survey demonstrating understanding as part of the consent process prior to enrollment. Specific recruitment procedures (e.g., local educational activities, community outreach, print- and web-based advertisements, etc.) will vary by site according to local needs. Strict ethical guidelines regarding professional conduct and confidentiality will be enforced for all study staff. Particular populations of interest to be targeted for recruitment include:

- Hospitalized patients. HIV outpatient clinic sites will be encouraged to partner with their affiliated inpatient institutions for recruiting these patients.

- Emergency Departments (EDs). Clinics will be encouraged to partner with local EDs for direct referral of patients presenting to the ED with opioid overdose.
- Persons utilizing local needle exchange and other sites that provide HIV testing for persons who inject opioids.
- Detox/addiction treatment facilities with HIV testing services.
- Local syringe exchange programs.
- People receiving services from community-based AIDS service outreach organizations.
- People being released from local criminal justice systems.

Enrolling participants in clinical settings poses many challenges to screening and interviewing potential participants [120-123], including the rapid pace of care, interruptions, clinic productivity requirements, space limitations, participants not feeling well enough, and the presence of multiple HIV care team staff members. To minimize the impact of these challenges, research staff will spend considerable time in participating HIV clinics interacting with staff, familiarizing themselves with clinic patient flow, and learning how to communicate and negotiate with clinic staff regarding the necessary space and time to conduct interviews.

Site PIs, who are HIV clinic providers or someone who has strong relationships with HIV providers, will facilitate negotiation of space and time requirements and be a resource to research staff regarding participating HIV clinic procedures. Staff and sites with experience and expertise in conducting research studies in outpatient HIV clinic settings will be prioritized for site selection. A review of 13 clinical trials conducted in the University of North Carolina Infectious Disease Clinic suggested that integrating a dedicated research screener in clinic operations facilitates trial enrollment [123]. The Lead Investigator's research team has experience successfully integrating clinical trial research teams with outpatient HIV clinic staff, enrolling 82% of HIV providers and 73% of their eligible participants in one recent trial [122].

The interviewer will negotiate the location of the interview as necessary to protect confidentiality and respect HIV clinic patient flow. If necessary, the potential participant will be given the option to participate in screening, consent, and interview procedures in a nearby exam room or staff/patient lounge if it is unoccupied, or to reschedule the interview at another time. If a participant feels ill during the interview, the interview will stop and be rescheduled. In the Lead Investigator's team's prior experience conducting research interviews in outpatient HIV clinics, the team found this level of flexibility achieved high levels of participation and did not impede the flow of usual HIV clinic activities [3, 29, 124].

Participants may undergo repeat screening within the appropriate amount of time after an initial screen-fail, per the discretion of the site PI and in accordance with the Manual of Operating Procedures.

7.4 Special Populations to Consider

This study is likely to enroll persons involved in the criminal justice system who are receiving HIV care at participating sites. The study will not recruit persons incarcerated/detained in a correctional facility or currently considered "prisoners" by local or state laws, but will not exclude parolees or probationers. At screening, prisoner status will be assessed using a streamlined

assessment based on the definition of a prisoner in 45 CFR 46.303(c). Throughout the study, prisoner status will be documented on the Criminal Justice case report form (CRF).

Those participants who become incarcerated during the course of their involvement with this study will continue to be followed to ensure safety and data integrity. All study interventions (XR-NTX or TAU) will be discontinued while the participant is incarcerated. If necessary for safety and with the permission of the participant, correctional facility officials will be informed of study participation. When possible, participants will be contacted to complete questionnaires and surveys, which would include safety checks. These visits can occur over the telephone or as in-person visits, whichever is more appropriate for the local research site and the correctional facilities' policies. The visits will only occur if confidentiality can be maintained. This generally assumes that in-person visits will be done in private rooms and that recording equipment (regardless of type of visit) can be turned off or destroyed. No biospecimens will be collected (blood or urine) during any visit that occurs with an incarcerated prisoner. If necessary, specific documents for incarcerated participants will be developed and approved by the IRB of record. All local guidelines will be followed, including any required reporting to the IRB or other institution when a participant becomes incarcerated. Despite the use of a central IRB for this study, local IRBs may be notified if a participant becomes incarcerated. Appropriate progress notes will be written to ensure complete documentation of any interaction with an incarcerated participant, specifically mentioning confidentiality procedures.

An Office for Human Research Protections (OHRP) Prisoner Research Certification Letter will be filed through the IRB of record and distributed to the sites that cede review. Sites that are not ceding review to the IRB of record will be responsible for obtaining an OHRP Prisoner Research Certification Letter. Local sites will be covered by the OHRP Prisoner Certification to enable follow-up of study participants who may become incarcerated.

Number of Sites

No more than eight HIV outpatient clinics will serve as sites for this study.

7.5 Site Characteristics

HIV clinics will be selected primarily on the basis of the following characteristics:

1) Provide HIV primary care.

2) Have a sufficient population of potential participants to achieve study enrollment goals.

3) Have providers willing to be trained in use of XR-NTX for management of opioid use disorder.

4) Capable of prescribing ART to participants, regardless of CD4 count.

5) Access to addiction counseling services as part of usual care.

6) Clinic offers access to opioid agonist treatment, either on-site or by referral.

We will specifically target HIV clinics in areas that have local prevalence of untreated opioid use disorder and HIV that support feasibility of enrollment.

7.6 Rationale for Site Selection

Sites that have access to an adequate number of HIV-infected participants with suboptimally controlled HIV and untreated opioid use disorder will be selected for participation. In order to achieve target enrollment for this study, we anticipate that most (but not all) participating HIV clinics will need to see ≥1,000 unduplicated HIV-infected potential participants per year. This number is based on enrollment rates observed in the pilot study and experience of CHOICES pilot study investigators in enrolling subjects in the BHIVES study [29]. We have also included site selection criteria that attempt to limit site variability in treatment effects (e.g., capacity for prescribing ART regardless of CD4 count; access to addiction counseling services).

7.7 Collaboration with CTSA for Site Recruitment

Site recruitment will explore opportunities to partner with the NIH-funded Clinical and Translational Science Award (CTSA) consortium. CTSA institutions work to transform local, regional, and national environment to increase the efficiency and speed of clinical and translational research. Potential opportunities for collaboration between CTN-0067 and affiliated CTSAs include CTSA assistance with community-based recruitment and/or some aspects of study implementation.

8.0 OUTCOME MEASURES

8.1 Primary Outcome Measures

The *primary outcom*e variable for CTN-0067 CHOICES scale-up study is HIV viral suppression. HIV viral suppression is defined as an HIV-1 RNA ≤ 200 copies/ml at 24 weeks. We are aware that, for participants on therapy, the goal of antiretroviral therapy is achieving a viral load "below the limit of detection of the assay" which currently is usually < 40 copies/ml. However, we have chosen to define "suppression" for this study as less than or equal to 200 copies/ml to be consistent with the January 2011 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [92]. The rationale for this definition is to avoid the influence of "blips" in HIV RNA viral load which commonly occur at levels between 40 and 200 copies/mL using current PCR assays and which are of limited clinical significance [125, 126].

8.2 Secondary Outcome Measures

1) Secondary HIV outcomes:

a. VACS Index. Change in VACS Index at 24 weeks compared with randomization. (score; derived from screening and week 24 laboratory and demographic data).

b. CD4 Count. Change in CD4 count at 24 weeks compared with randomization (count; laboratory assay).

2) Engagement in HIV Care:

a. ART Prescribed. Proportion of participants prescribed ART within 24 weeks following randomization (binary; medical record abstraction).

b. ART Adherence. Proportion of participants taking 100% of prescribed ART doses in the past month at 24 weeks for those prescribed ART at any point during the 24 week trial (binary; self-reported VAS medication adherence measure).

c. Retention in HIV Care. Proportion of participants with at least 1 HIV primary care visit in the past 12 weeks, measured at week 24 (binary; medical record abstraction).

d. HIV Risk Behaviors. Past 30 day injection drug use, unprotected sex, multiple sexual partners as measured by the RAB at week 24 (binary; self-report).

e. Quality of life. Past 30 day health-related quality of life as measured by EQ-5D at week 24, compared to baseline.

3) ART Adherence Mediation Variables:

a. Days of Opioid Use. Number of days of opioid use since baseline, as measured by Timeline Follow Back (TLFB) at 24 weeks (count; self-report).

b. Opioid Abstinence. Past 30 day opioid abstinence (by Addiction Severity Index (ASI)-lite self- report, Time-Line Follow-Back (TLFB) and urine drug screen (UDS) confirmation) in the final 30 days of the 24 week trial (binary; self-report + UDS).

9.0 STUDY PROCEDURES

9.1 Duration of Participant Study Procedures

9.1.1 Pre-screening

Individuals will be approached by study staff in HIV clinic settings or referred to study staff by HIV clinical care and outreach teams. Study staff will provide a brief verbal overview of the study to the individual and provide written information regarding XR-NTX. Individuals will provide verbal consent and HIPAA Authorization/Waiver as necessary for pre-screening and will be asked to complete the Pre-Screening Interview. This verbal consent and HIPAA Authorization/Waiver will only apply for the Pre-Screening visit. The Pre-Screening Interview will elicit information about the potential participant's demographics and drug use. The Pre-screening informed consent, HIPAA Authorization/Waiver (if necessary), and pre-screening interview will take approximately 5, 5, and 10 minutes to complete, respectively. Individuals who undergo pre-screening will be captured on the Pre-Screening Log.

9.1.2 Figure 3. Study Duration

Activity:	Screening & Enrollment	Active Treatment	Total Participant Time in Study
Duration:	1-4 weeks	24 weeks	25-28 weeks

9.1.3 Screening and Enrollment Procedures (1-4 weeks duration)

Once a person has completed the Pre-Screening Interview process and meets basic eligibility criteria, they will either be asked to stay for the Screening Visit or scheduled to come back for the visit (based on staff and candidate's availability). It is expected that the screening and enrollment phase will take approximately 1-4 weeks; however, participants will have 60 days from the date of consent to complete screening and be randomized before being considered a screen failure.

9.1.4 Informed Consent Process

Study procedures and the potential risks and benefits of participating in the trial will be explained by research staff. Staff will be available to answer questions about the consent form and consent quiz while participants are reviewing them. After signing the consent form, participants will be given a copy of the form to keep for their records. The process will take approximately 20-30 minutes.

9.1.5 Locator Form

Participants will complete a locator information form which will be used to contact them to remind them of follow-up visits, as well as to locate participants who may not have attended appointments. When completing this form, participants provide their names, addresses, and telephone numbers as well as contact information for at least two other persons. Permission will also be requested to obtain locating information from additional agencies and publicly accessible databases or search engines including, but not limited to, Medicare/Medicaid and Social Security offices, department of motor vehicles, local jail logs, white pages, and Facebook. Locator information will be reviewed at each visit and updated as needed during the study. The locator

information form will take approximately 5-10 minutes to initially complete and content will be checked at future study visits.

9.1.6 Medical Record Release Form

Participants will complete the form(s) as applicable during screening and throughout the study to grant permission to study staff to review inpatient, outpatient, mental health, and substance use treatment clinic records as needed. The purpose of medical record review at the end of study participation is to document information needed to evaluate secondary outcomes. Specifically, study staff will abstract medical record information to corroborate participants' self-report of information including, but not limited to the following: HIV viral load and CD4 count, liver enzymes, hepatitis B and C serologies, CBC, metabolic panel, INR, utilization of HIV primary care, utilization of HIV and addiction treatment services, and opioid overdose events. Records review/abstraction will occur throughout the study (as needed) and up to 52 weeks post-randomization.

9.1.7 Collection of Biological Specimens

Study staff will collect blood specimens at screening, randomization, 12 weeks, and 24 weeks to confirm eligibility and assess the primary outcome of HIV-1 RNA PCR and secondary outcomes of CD4 count, VACS Index, and hepatotoxicity. CBC, serum creatinine, LFTs (AST, ALT), INR, and HIV-1 RNA blood specimens will be collected during screening. CD4, Hepatitis C, Hepatitis B, and PBMC specimens will be collected and processed only after the participant has been randomized. Study staff will collect urine specimens during screening and at treatment initiation (XR-NTX arm only), safety visit (XR-NTX arm only), and at 4, 8, 12, 16, 20, and 24 weeks to confirm eligibility and assess secondary outcomes and pregnancy. Screening and randomization labs (CD4, HIV-1 RNA, and hepatitis B and C serologies) drawn in the 90 days prior to date of informed consent may be abstracted from participant medical records, when available. Other screening lab tests may be abstracted from medical records if drawn within 30 days prior to the date of informed consent, with the exception of urine specimens, which must be collected by study personnel. Some participating sites may require that copies of some or all lab results collected for study purposes be filed in participants' medical records.

9.1.8 Baseline Assessment

After the enrollment process is complete, study staff will prepare a new data record for the participant and the baseline assessments will be administered either through a computer-assisted data collection instrument or a paper version of the CRF. The baseline assessments are detailed in Section 10.0 and capture participant medical, psychiatric, and drug use history, HIV status and care, quality of life, current health status, and other baseline characteristics. The baseline assessment will take approximately 60-90 minutes to complete.

9.1.9 Randomization

The timing of randomization will follow shortly after baseline assessments and final confirmation of eligibility. Participants will be encouraged to initiate treatment within 28 days of randomization. If a participant is unable to initiate treatment within 28 days, he or she may initiate XR-NTX study drug at any time until week 20 and may initiate TAU at any time during the trial. Initiation of assigned treatment will be tracked.

Participants will be randomized in a 1:1 fashion to either office-based XR-NTX or TAU using a permuted block design with randomly-sized blocks. Randomization will be stratified only by site. Participants who meet DSM-5 criteria for both opioid and alcohol use disorder (16% of CTN-0055 CHOICES pilot study participants) will be included, in addition to participants with OUD, alone.

Concomitant alcohol use disorder will be considered as a potential covariate [31], [127, 128]. Participants need not be abstinent from opioids at the time of randomization.

The randomization procedure will be conducted in a centralized process through the Data and Statistics Center (DSC). Specifically, randomization schedules will be created by the study statistician for each site. The randomization schedules will be of a randomized-block nature to ensure relative equality of assignment across condition across the recruitment period and to prevent the potential for study staff guessing the next assignment, which is heightened when a fixed block-size is used. After the baseline assessment is successfully completed, a designated site study staff member will perform the randomization. Randomization for each participant is done over the internet using the Enrollment Module in Advantage eClinical.

The DSC statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new participant due to the intent-to-treat nature of the study.

9.2 Treatment Conditions

9.2.1 HIV Usual Care (Both Arms)

All participants will receive comprehensive HIV primary care, case management, addiction counseling, and social support services from HIV clinics as they would regardless of study participation. As part of protocol training, HIV clinic providers will be encouraged to offer ART within 4 weeks of randomization for participants not already prescribed ART. Current guidelines recommend offering ART to all HIV-infected participants, regardless of CD4 count [35]. The schedule of medical care provided will be as deemed appropriate by the treating provider. HIV-infected participants are typically seen at least twice within the first month of initiating ART, and at least every 3 months thereafter for monitoring. Medical visits will not be considered study visits, though they may coincide with study visits. HIV clinic treatment will also include usual addiction counseling services, which are offered as a part of usual care in most large U.S. HIV clinics. As part of protocol training, HIV clinic providers will be asked to refer study participants to existing addiction counseling services in their clinic, as they would do regardless of study participation. Throughout the course of the trial, HIV clinics will be monitored for any potential changes that might occur in standard practice around medical management of HIV infection or addiction treatment services. Throughout study participation, HIV clinic medical visits will be tracked through medical record abstraction, and counseling visits will be tracked through participant self-report (See Section 10, Assessments).

9.2.2 Medical Management (when applicable)

Study clinicians will be trained in medical management (MM). MM is a brief counseling intervention delivered by non-addiction medical providers to improve response to medication-assisted addiction treatments delivered in medical settings [129] [130]. It has augmented care for medication-assisted treatment of alcohol dependence with acamprosate and oral naltrexone in the COMBINE study [131], integration of XR-NTX treatment of alcohol dependence in primary care settings [36], and integration of BUP/NX for treatment of opioid dependence in primary care [132]. Since MM is meant to facilitate medication-assisted addiction treatment, it will be performed only for participants offered medication-assisted treatment in the HIV clinic (e.g., participants with opioid use disorders randomized to XR-NTX and TAU participants receiving clinic-based buprenorphine/naloxone or methadone for opioid use disorder). TAU participants referred for off-site methadone maintenance or buprenorphine/naloxone will not receive MM since medical

oversight is the responsibility of the treating provider. TAU participants who receive non-medication-assisted treatments such as 12-step groups or psychosocial counseling will not receive MM. During brief MM sessions, study clinicians will review recent drug and alcohol use, recommend abstinence, review medication side effects, and encourage adherence to medication-assisted treatment and participation in clinic and/or community support groups.

9.2.3 Clinic-based Extended-Release Naltrexone (XR-NTX)

9.2.3.1 XR-NTX Detoxification and Induction (0 - 4 weeks duration, during active treatment phase)

Following randomization, participants assigned to office-based XR-NTX will undergo detoxification and naltrexone induction in accordance with the package insert and published guidelines [133-136]. Participating HIV providers will be trained to manage outpatient detoxification procedures for participants with mild to moderate anticipated opioid withdrawal severity. Provider training reviews a range of detox options outlined in the Manual of Operating Procedures [137, 138]. Participants failing an induction regimen and those with anticipated severe withdrawal may be referred to local detox facilities for medication-assisted inpatient detoxification.

9.2.3.2 Active Treatment with XR-NTX (Treatment Initiation through Week 20)

XR-NTX (4cc, ~380mg of naltrexone base) will be administered *approximately* every four weeks (treatment initiation visit and weeks 4, 8, 12, 16, and 20) for an approximate maximum of 6 doses in the form of Vivitrol®, which will be obtained by NIDA or the NIDA contractor for distribution to the sites. Administration of XR-NTX more frequently will require approval by the Lead Investigators and will be provided on a case-by-case basis. XR-NTX will be administered by intramuscular injection to the buttocks (alternating sides monthly) according to the injection preparation and administration procedures specified in the Vivitrol® product package insert. These procedures are designed to minimize the risk of injection site reactions.

9.2.3.3 Handling of Missed XR-NTX Doses, Lapses, and Relapses

Use of illicit opioids presents different concerns in the management of participants receiving XR-NTX maintenance, compared to those participants receiving agonist therapy. A participant receiving XR-NTX may miss a scheduled injection and resume opioid use. However, because of the long duration of action of XR-NTX (full blockade out to 5 weeks after the last injection [101]), a grace period of at least 7 days after the scheduled injection can be expected during which repeat XR-NTX injection can be rescheduled without risk of relapse. If the participant misses a scheduled injection and uses opioids during at least two of the seven days following the date of the scheduled injection, relapse will be suspected and the provider will perform a repeat naloxone challenge as described in the Manual of Operating Procedures. If the challenge is negative, XR-NTX administration will be resumed. If positive, then XR-NTX administration would risk precipitating withdrawal. However, because naltrexone blood levels remain and there is partial blockade beyond week 5, vulnerability to relapse may be more gradual, and the possibility of mild or equivocal reactions to naloxone challenge more common. In this instance, a second challenge within 72 hours will be attempted, and, if tolerated, the next injection can be given. Missing a scheduled XR-NTX injection is the most important threat to the success of naltrexone maintenance. In the event that a participant misses a scheduled injection, clinic study staff will contact the participant for follow-up. The goal of these contacts is to re-establish commitment to XR-NTX treatment and schedule the next injection as soon as possible. Participants who miss a scheduled XR-NTX dose but remain abstinent (i.e., return to clinic reporting no opioid use, urine negative for all opioids, and passing naloxone challenge), may be restarted on XR-NTX up to 3 weeks after the scheduled dose.

Among the 9 individuals in the pilot study who had opioid use disorder and were unsuppressed at baseline, 6 (17%) of the 36 subsequent viral load values were missing. In the pilot, viral load was measured monthly, increasing the opportunity for missing data, whereas CTN-0067 collects follow-up viral loads only at 12 and 24 weeks and will likely have fewer missing viral loads. The primary outcome analysis will be carried out using the binary repeated measures of viral load (RMVL) framework of Rose et al., a type of time series model. In theory, time series models can accommodate missing data better than non-longitudinal models by using all non-missing data points. However, this approach assumes that missing data are not informative, that is, that missing values are probably similar to corresponding non-missing values with the same set of other predictors. For substance-use trials, missing at random (MAR) is less likely than missing not at random (MNAR) alternative: if data are missing, it is probably because the participant is unsuppressed. So, for the primary analysis, “unsuppressed” will be substituted for missing suppression status values. Since death is at least as undesirable as lack of suppression, “unsuppressed” will be assigned as a status value for visits subsequent to death. A secondary sensitivity analysis will explore the extent to which trial conclusions need to be changed as the missingness assumption approaches MAR.

9.2.3.4 Dispensing of XR-NTX

Study medication (XR-NTX) will be provided by the study at no cost to the participant. XR-NTX will be administered in clinic at the Treatment Initiation Visit and at treatment weeks 4, 8, 12, 16 and 20.

9.2.4 Treatment as Usual (TAU)

Participants assigned to the TAU group will receive the standard treatment for opioid use disorder provided at each HIV clinic. The standard of care in U.S. HIV clinics is currently to link with opioid agonist treatment services. Opioid substitution therapy is recommended for HIV-infected participants with opioid dependence [35, 104], and many HIV practices are being encouraged to adopt clinic-based BUP/NX [105]. Assessment of TAU includes assessing use of medication-assisted treatments for alcohol use disorder as well as opioid use disorder since we anticipate some participants with OUD will also have AUD. TAU assessment will also include characterization of usual counseling services and linkages with local detox programs available at each site.

Many HIV clinics receive funding from the Ryan White Care Act for case management and addiction/mental health counseling services to facilitate engagement of HIV-infected patients with substance use disorders in treatment. In a 6-month randomized trial of methadone maintenance referral strategies, passive referral of heroin users resulted in 8% methadone maintenance enrollment at 6 months vs. 29% enrollment among those randomized to case-management assisted referrals ($p = .006$) [139].

During the formal site selection process, a thorough assessment will be conducted of each site’s standard practice for linkage to addiction treatment services. Throughout the course of the trial, HIV clinics will be monitored for any potential changes that might occur in standard practice around linking HIV-infected clinic patients to substance use treatment.

9.3 Ancillary Treatments

Participants who experience withdrawal symptoms or nausea associated with detoxification and induction may be treated with ancillary medications (see guidelines in study Manual of Operating Procedures (MOP)). Depression is also common in opioid-dependent participants and, though not causally related to XR-NTX use, may adversely affect prognosis of naltrexone treatment [140,

141]. Participants who show depressive symptoms may be treated by their HIV clinic providers with antidepressants and/or referred for mental health evaluation and treatment.

9.4 Provisions for Access to Treatment after Study

Prior to the conclusion of the 24 week active treatment phase, the research team will make an effort to arrange for continued treatment with XR-NTX as locally available and appropriate. In most cases, the study physician will continue to prescribe this FDA-approved study medication as the participant's HIV primary care provider. Where this is not possible (due to insurance or availability of treatment resources, etc.), alternative treatment referrals (e.g., methadone maintenance, intensive outpatient psychosocial aftercare), special access programs, and manufacturer medication assistance plans will be made as appropriate.

9.5 Drug Packaging / XR-NTX

XR-NTX will be supplied in single use kits. Each kit will contain one 380 mg vial of Vivitrol® microspheres, one vial containing 4 mL (to deliver 3.4 mL) diluent for the suspension of Vivitrol®, one 5-mL prepackaged syringe, one 1-inch 20-gauge needle, two 1.5-inch 20-gauge needles and two 2-inch 20-gauge needles with needle protection devices. The lot number will be included on the kit labels as supplied by the manufacturer.

9.6 Participant Discontinuation

All participants will be followed for the duration of the study (25-28 weeks, depending on length of time required for completion of screening and enrollment procedures) unless they withdraw consent, or the investigator or sponsor decides to discontinue their enrollment. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons.

9.7 Blinding

CTN-0067 is an unblinded study.

9.8 Participant Compensation

Participants will be compensated for their time and effort for baseline and follow-up visits. Participants may receive a maximum amount of up to approximately $510.00 U.S. Dollars for completing the following activities: screening interview, baseline assessment, and visits at 1, 4, 8, 12, 16, 20, and 24 weeks. The specific amounts and format (e.g., cash, debit card, voucher, etc.), and distribution schedule will be determined by the participating site with the approval of the Lead Investigator or Co-Lead Investigators and the IRB. All compensation will be recorded and tracked in the Compensation Log.

9.9 Long Term Mortality Follow-up

In the future, we will attempt to account for all participants who may have died after the study ends. We will do this by sending participant data to the National Center for Health Statistics' (part of the Centers for Disease Control and Prevention) National Death Index. This is a list of all persons who have died in the U.S. Data, if available, will be abstracted from the Locator Form and other CRFs and may include name, date of birth, sex, race/ethnicity, social security number, state of residence, date of last contact, and date of death. The date and cause of death identified

by the National Death Index will be entered into a secure database at OHSU. Information regarding persons presumed to still be alive in the National Death Index will be destroyed.

10.0 STUDY ASSESSMENTS AND INSTRUMENTS

The selected assessments attempt to balance the value of comprehensive data against the costs of data collection in terms of staff time, feasibility of completing assessments in an outpatient HIV clinic setting, financial cost, and response burden. Therefore, assessments have been limited to those that contribute directly to the study objectives or that are necessary for reasons of safety or regulatory compliance. When choosing between comparable instruments, we have chosen instruments for which CRFs have already been built for other recent CTN trials to minimize the cost of new CRF construction.

10.1 List of all CRFs and Table of Assessments

Assessment/Activity	Pre-Screening	Screening	Baseline	Random-ization^^	Treatment Initiation	Safety Visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	End of Study (≠Week 24)	As Needed
Enrollment														
Pre-Screening Verbal Consent and HIPAA Authorization/Waiver	X													
Pre-Screening Interview	X													
Demographics (from PhenX)		X												
Master Enrollment Log++		X	X											
Informed Consent/HIPAA		X												
Inclusion/Exclusion Checklist				X										
Locator Form++		X	X	X	X	X	X	X	X	X	X	X	X	
Medical Release++		X												X
Study Administration														
Inventory Form														X
Pre-screening Log++	X													
Secure Document Upload		X												X
Missed Visit Form														X
Progress Note Checklist++		X	X	X	X	X	X	X	X	X	X	X	X	
Protocol Deviation														X
Visit Compensation Log++		X	X	X	X	X	X	X	X	X	X	X	X	
End of Treatment												X		X
Study Completion												X		X
Safety and Medical Measures														
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X
ARV Medication Log			X									X	X	
Concomitant Medications		X												
CBC		X										X	X	
CD4 Count				X					X			X	X	
Serum Creatinine		X										X	X	
Confirmed Pregnancy and Outcome														X
Detoxification					X									
Fatal Opioid Overdose														X

Assessment/Activity	Pre-Screening	Screening	Baseline	Random-ization^^	Treatment Initiation	Safety Visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	End of Study (≠Week 24)	As Needed
Vital Signs (blood pressure, pulse, temperature, height and weight)		X										X±	X±	
Hepatitis B surface antigen (HBs AG)				X										
Hepatitis C virus antibody (HCV ab)				X								X**		
Hepatitis C PCR confirmation, when HCV ab +				X**								X**		
HIV-1 RNA PCR		X							X			X	X	
LFT (AST, ALT) and INR		X							X			X	X	
Medical and Psychiatric History		X												
Medication Adherence			X		X		X	X	X	X	X	X	X	
Pain Assessment			X				X	X	X	X	X	X	X	
Non-Fatal Opioid Overdose			X									X	X	
PBMC				X					X			X	X	
Physical Examination		X												
Pregnancy and Birth Control Assessment (including urine pregnancy test)		X			X*,^	X*,^	X	X	X	X	X	X	X	
Naloxone Challenge*														X
XR-NTX Administration Log* ++					X		X	X	X	X	X			
XR-NTX Injection*					X		X	X	X	X	X			
Injection Site Abnormality*														X
Injection Site Examination*						X	X	X	X	X	X	X	X	
ASI Lite Drug/Alcohol Use			X									X	X	
Concise Health Risk Tracking – Self Report		X			X	X	X	X	X	X	X	X	X	
Concise Health Risk Tracking – Clinician Rated														X
DSM-5 Substance Use Disorders		X												
Urine Drug Screen		X			X*	X*	X	X	X	X	X	X	X	
HIV Care Utilization			X									X	X	
Buprenorphine and Methadone Chart Abstraction							X	X	X	X	X	X	X	
Quality of Life, from PhenX			X											
Quality of Life, from EQ-5D			X									X	X	

Assessment/Activity	Pre-Screening	Screening	Baseline	Random-ization^^	Treatment Initiation	Safety Visit	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	End of Study (≠Week 24)	As Needed
Risk Assessment Battery			X				X	X	X	X	X	X	X	
Tobacco Use History and Substance Use History, from PhenX			X									X	X	
Timeline Follow Back			X		X		X	X	X	X	X	X	X	
Treatment Plan				X			X	X	X	X	X	X	X	
Treatment Initiation***													X	X
XR-NTX Non-Initiation*														X
Treatment Satisfaction Survey												X	X	
Treatment Services Review			X		X		X	X	X	X	X	X	X	
VACS Index				X								X	X	
Visual Analog Scale			X				X	X	X	X	X	X	X	
PHQ-9 Depression Symptoms			X						X			X	X	
Suicidal Risk														X
Criminal Justice			X						X			X	X	
Participant Treatment Preference			X											

** Only for participants randomized to the XR-NTX arm.*

***At randomization, HCV PCR confirmation is required when HCV ab is positive. At 24 weeks, collect HCV ab if participant tested HCV ab negative at randomization or if HCV ab result was not obtained at randomization. At 24 weeks, collect HCV PCR confirmation if: HCV antibody is positive at randomization, but HCV PCR was not obtained at randomization or HCV antibody was negative at randomization, but HCV antibody is positive at Week 24.*

**** Only for participants randomized to TAU arm.*

± Height and weight only for BMI calculations.

++ Not captured in eClinical.

^Urine pregnancy test required for XR-NTX group only; remainder of Pregnancy and Birth Control Assessment required for all participants.

^^Assessments performed at randomization correspond with Week 0 requirements in the eClinical system.

11.0 HIV-RELATED MEASURES

11.1 Antiretroviral Medication Prescription and Adherence

Since HIV viral suppression is most strongly influenced by optimal use of ART, evaluation of adherence to one's ART regimen is essential. Self-reported antiretroviral use and adherence will be assessed using a Medication Adherence questionnaire with visual analogue scale [142, 143] that is administered at baseline, treatment initiation, and weeks 4, 8, 12, 16, 20 and 24 weeks or the end of study visit (if not week 24) for assessment of secondary outcome if participant is prescribed ART at the time of follow-up visits. The Medication Adherence questionnaire asks the participant about adherence to HIV medications in the past month. We will assess the proportion of participants taking 100% of prescribed ART doses, based on visual analogue scale responses, in the past month at baseline, treatment initiation, and weeks 4, 8, 12, 16, 20, and 24 for those prescribed ART (proportion; self-reported medication adherence measure).

Because self-reported use of specific antiretrovirals has limited reliability when compared with medical record review [144, 145], we will confirm ART use with medical record review at baseline and 24 weeks (or the end of study visit, if not week 24) using the ARV Medication Log to assess the secondary outcome of ART prescription. Specifically, we will assess change in the proportion of participants prescribed ART within 24 weeks following randomization, compared to baseline (binary; medical record abstraction).

11.2 HIV Care Utilization

Study staff will assess the number of HIV primary care visits at baseline and 24 weeks, or the end of study visit, if not week 24 (count, chart abstraction).

11.3 HIV Risk Assessment Battery

The Risk Assessment Battery (RAB) [146] is a self-administered assessment of engagement in activities that increase the likelihood of HIV transmission. Only sexual and drug-related HIV risk behavior items will be included, in an effort to limit instrument redundancy and participant response burden. Several scores that measure drug risk, sex risk, and total risk will be computed. It will be assessed at baseline and at weeks 4, 8, 12, 16, 20, and 24 (or the end of study visit, if not week 24).

11.4 VACS Index

The VACS Index is a validated biomarker score that reflects overall health and is a potent predicator of mortality in HIV-infected patients [147, 148]. The VACS Index is calculated by summing scores for age, CD4 count, HIV-1 RNA, hemoglobin, liver fibrosis (FIB-4), renal function (eGFR), and HCV status (**Table 11.1**) [148, 149]. It is responsive to abstinence among HIV-infected patients receiving opioid agonist treatment even when they enter such treatment with an undetectable HIV viral load [150]. A clinically meaningful difference is 5 points as it relates to a 20% change in 5-year mortality risk [147-149]. It will be assessed at randomization and week 24, or the end of study visit, if not week 24.

11.5 Table 1: Point Values Used to Calculate VACS Index

Component		VACS Index
Age	<50	0
	50-64	12
	≥65	27
CD4	≥500	0
	350 to 499	6
	200 to 349	6
	100 to 199	10
	50 to 99	28
	<50	29
HIV-1 RNA	<500	0
	500-1x10^5	7
	>1x10^5	14
Hemoglobin	≥14	0
	12 to 13.9	10
	10 to 11.9	22
	<10	38
FIB-4	<1.45	0
	1.45 to 3.25	6
	>3.25	25
eGFR	≥60	0
	45 to 59.9	6
	30 to 44.9	8
	<30	26
Hepatitis C		5

Definitions:

- FIB-4 = (years of age x AST in U/L) ÷ (platelets in 10^9/L x square root of ALT in U/L)
  - Measure of liver fibrosis
- eGFR = 186.3 x (serum creatinine$^{-1.154}$) x (age$^{-0.203}$) x (0.742 for women) x (1.21 if black)
  - Estimated glomerular filtration rate; Measure of renal function

12.0 GENERAL MEASURES

12.1 Inclusion/Exclusion

This form will include each inclusion and exclusion criterion to document eligibility. Eligibility will be assessed prior to randomization, and then continually as appropriate. Only participants who continue to meet study eligibility criteria will be allowed to continue with the screening process and randomization.

12.2 Locator Form

A locator form will be used to obtain information to assist in finding participants during screening/baseline and at follow-up. This form will collect participants' current address, email address, and phone number(s). In order to facilitate locating participants if direct contact efforts are unsuccessful, we will attempt to collect addresses and phone numbers of 2-3 family/friends, who may know how to reach the participant, as well as information such as Social Security number, driver's license number, social media, and other information to aid in searches of public records. This information will be collected at screening and will be updated at each visit. No information from this form will be used in data analyses.

12.3 PhenX Core Tier 1 Forms

The Substance Abuse and Addiction Collection of the PhenX Toolkit (www.phenxtoolkit.org) includes highly recommended measures that are being adopted across NIDA-funded research. The Core Tier 1 collection includes measures for demographics (age, ethnicity, sex, race, educational attainment, employment status and marital status), BMI, quality of life, and HIV Risk & Status; substance use measures include age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco and other substances. We will delete Core Tier 1 items regarding HIV testing, since only HIV-infected participants are eligible for the current study. Core Tier 1 assessments will be completed at baseline only, with BMI and tobacco use questions repeated at week 24 or the end of study visit, if not week 24.

12.4 Demographics Form

The demographics form will collect information about demographic characteristics of the participant, including sex, date of birth, ethnicity, race, education, employment pattern, and marital status. The PhenX Core Tier 1 form will be completed during the screening process to collect demographic data.

12.5 Treatment Satisfaction Survey

Satisfaction with treatment will be recorded on the Treatment Satisfaction Survey completed at week 24 visit or the end of study visit, if not week 24.

12.6 Treatment Plan

This form will be used once the participant is randomized. After randomization, the participant will meet with the study clinician to develop a plan that will determine the activities the participant should engage in, including addiction pharmacotherapy (e.g., methadone, buprenorphine, XR-NTX) during the active treatment phase of the protocol. This meeting and form should be completed the same day the participant is randomized. The Treatment Plan will be reviewed at follow-up visits 4, 8, 12, 16, 20, and 24 or the end of study visit, if not week 24.

12.7 Medication Adherence

This form will track the participant's adherence to recommended addiction pharmacotherapy (i.e., methadone, buprenorphine, or XR-NTX) as described in the Treatment Plan.

12.8 End of Treatment Form

This form tracks the participant's status with regards to the study intervention/medication or treatment(s) received as part of TAU. It will be completed if the participant permanently stops treatment early or at the week 24 visit (for participants who complete study participation) or at the end of study visit (for participants who permanently stop the study trial early).

12.9 Study Completion Form

This form tracks the participant's status in the study. It will be completed at the week 24 visit, once the week 24 visit window elapses for participants who do not complete this final visit or after the week 24 visit is completed for participants who complete the final visit, or once the site confirms that a participant is permanently done with the study (i.e., participant died or withdrew consent). This form will be used in data analyses to address variables such as treatment retention and completion.

12.10 Treatment Initiation and XR-NTX Non-Initiation

The Treatment Initiation form will track participants randomized to the TAU arm only and will track initiation of TAU. This form will be completed once the participant reports that they have intitated TAU treatment. If treatment is not initiated, the form must be completed by end of study.

The XR-NTX Non-Initiation form will track non-initiation of XR-NTX injections for participants randomized to the XR-NTX treatment arm. This form will be completed as needed if a participant does not receive any XR-NTX injections. If the participant receives *at least* one injection, this form will not be completed.

13.0 SAFETY AND MEDICAL MEASURES

The study clinician must review and approve all safety and eligibility assessments to confirm participant eligibility prior to randomization.

13.1 Medical and Psychiatric History

The study clinician will obtain a medical and psychiatric history from the participant covering past and present health conditions to help determine eligibility and to provide baseline information. This form will be collected during screening. Information from this form may be used in data analyses.

13.2 Physical Examination

The study clinician will complete a physical examination at screening, to ensure that there are no medical concerns regarding participation and to gather baseline information regarding the participant's physical health. During the screening physical exam, a description of the participant's body habitus will be documented, and the study clinician will examine the planned injection sites to ensure adequacy for XR-NTX gluteal intramuscular injection of naltrexone with the supplied needle.

13.3 Vital Signs

Study personnel will complete vital signs (blood pressure, pulse, temperature, height, and weight) at screening to inform overall medical fitness for participation, along with the physical exam. Height and weight only will be collected at week 24 or the end of study visit, if not week 24.

13.4 DSM-5 Checklist

The DSM-5 Checklist is a semi-structured, interviewer-administered instrument that provides current diagnoses for substance use disorders based on DSM-5 diagnostic criteria. The DSM-5 Checklist will be completed at screening to determine eligibility.

13.5 Clinical Laboratory Tests

Trained staff will be responsible for collecting and processing biologic specimens. Local laboratories at participating sites will be used to conduct all laboratory tests with the exception of the PBMCs. Laboratories must participate in the Clinical Laboratory Improvement Act of 1998 (CLIA) or be accredited by the College of American Pathologists (CAP). If neither CLIA nor CAP is available, equivalent evidence of laboratory certification may be acceptable and must be discussed on a case-by-case basis with the Lead Team. Laboratories should provide reference ranges and proof of laboratory certification.

HIV-1 RNA PCR: will be drawn at screening, 12, and 24 weeks (or the end of study visit, if not week 24) for outcomes assessment. At screening, results of laboratory tests conducted within 90 days prior to date of informed consent will be acceptable.

CD4 Count (T-helper cells): will be drawn at randomization and at 12 and 24 week visits or the end of study visit, if not week 24, for secondary outcomes assessment. At randomization, results of laboratory tests conducted within 90 days prior to date of informed consent will be acceptable.

Peripheral Blood Mononuclear Cells (PBMCs): For all randomized participants (both TAU and XR-NTX), we will collect four 8mL or eight 4mL CPT tubes for PBMC analysis at randomization,

12, and 24 (or end of study visit if not week 24). Blood draws may coincide with other research blood draws. PBMC analysis will be conducted in a related NIH application to assess the effects of opioid blockade on TLR mediated immune responses at a later time. PBMC samples will be shipped to a lab at Oregon Health & Science University and kept indefinitely. PBMC samples will be used for immunologic testing. It is also possible that banked PBMC specimens will be shared with other investigators for performance of genetic testing in the future.

Safety labs: AST, ALT, CBC, INR, serum creatinine, and urine pregnancy test (for all females) will be performed to help determine eligibility at screening. Receipt and review of laboratory test results is necessary before confirming eligibility, conducting randomization and starting study medication. Results of laboratory tests (not including urine pregnancy) conducted within 30 days prior to date of informed consent (e.g., collected as part of routine detoxification admission) will be acceptable. Urine pregnancy test will be repeated at the Treatment Initiation Visit (required for XR-NTX arm only), the safety visit (required for XR-NTX arm only), and weeks 4, 8, 12, 16, 20, and 24 (or the end of study visit, if not week 24). AST, ALT, CBC, INR and serum creatinine will be repeated at week 24 or the end of study visit, if not week 24.

Liver profile: AST, ALT, and INR will be repeated at the Week 12 and Week 24 visits (or the end of study visit, if not Week 24). This is consistent with recent studies supporting the lack of hepatotoxicity in patients receiving XR-NTX that led to dropping of the previous FDA black box warning regarding hepatoxicity.

Hepatitis: Blood will be collected at randomization for Hepatitis B surface antigen (HBsAG) and Hepatitis C virus antibody (HCVab) with reflex hepatitis C RNA PCR testing if antibody positive. These tests do not determine eligibility. Results of laboratory tests conducted within 90 days prior to date of informed consent (e.g., collected as part of routine detoxification admission) will be acceptable.

13.6 Pregnancy and Birth Control Assessment

This form will document the administration of pregnancy tests, test results, and female participants' self-reports of an acceptable method of birth control. The pregnancy and birth control assessment form, including on-site urine pregnancy tests, will be collected at screening. Birth control assessment and a urine pregnancy test will be repeated at the Treatment Initiation Visit prior to study drug induction (urine pregnancy test required for XR-NTX arm only), the safety visit (urine pregnancy test required for XR-NTX arm only) and the 4, 8, 12, 16, 20, and 24 week visits or the end of study visit, if not week 24. This will correspond to medical visits for repeat study drug dosing and a final assessment at week 24 or the end of study visit, if not week 24.

13.7 Injection Site Examination

The study clinician will examine the injection site on the next visit following each XR-NTX administration and document this on the Injection Site Examination form. The study clinician will also examine the injection site per standard of care before administering a new injection. Participants will be asked to immediately report any injection site reactions to study staff for evaluation, monitoring, and possible referral, as needed. Injection site reactions will be documented on the Injection Site Abnormality Log.

13.8 Pain Assessment

Pain assessment will occur at baseline, 4, 8, 12, 16, 20, and 24 weeks (or the end of study visit, if not week 24). Participants will be assessed for experiences of pain during the past 4 weeks

using the 3-item PEG [151]. The PEG asks respondents to estimate on a scale of 0 to 10 their average pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G). Participants will also be asked how pain was managed.

14.0 SUBSTANCE USE AND MENTAL HEALTH COVARIABLES

14.1 Urine Drug Screen

Urine drug screens will be collected at screening, study drug induction (Treatment Initiation Visit – required for XR-NTX arm only), safety visit (required for XR-NTX arm only), and 4, 8, 12, 16, 20, and 24 weeks (or the end of study visit, if not week 24) for assessment of secondary outcomes. All urine specimens will be collected using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. A further validity check will be performed using a commercially available adulterant test strip. The UDS will test for the presence of the following drugs: opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamines, marijuana, methadone, buprenorphine, phencyclidine (PCP), fentanyl and ecstasy (MDMA). The PCP result will not be recorded in the data system. The UDS will also test for ethyl glucuronide (EtG), which is a biomarker of alcohol consumption in the previous 22 to 31 hours and will be used to confirm self-reported alcohol abstinence [152, 153]. The UDS will be performed using various commercially available single or multi-panel tests. In the event urine specimen tampering is suspected, either based on observation or the adulterant tests, study staff should request a second urine sample, directly observed or according to clinic SOPs.

14.2 Addiction Severity Index-Lite (ASI-Lite) Drug and Alcohol Use

The ASI-Lite is derived from the Fifth Edition of the ASI [154], a structured clinical interview that yields scores for seven areas of functioning typically impacted by addiction, including medical status, employment status, drug use, alcohol use, family status, legal status, and psychiatric status. Only the drug use and alcohol use sections of the ASI-Lite will be used. Opioid use questions, including the main type of opioid used by the participant, whether a prescription opioid or heroin, the onset of the use, the participant’s perception of the substance that is most problematic, and their present treatment goal will also be assessed at baseline as part of the ASI-Lite assessment. The ASI-Lite drug and alcohol sections will be completed at baseline and 24 weeks (or the end of study visit, if not week 24) for assessment of secondary outcomes.

14.3 Timeline Follow Back (TLFB)

Timeline Follow Back (TLFB) assesses self-reported drug and alcohol use over the past 30 days, with high test-retest reliability and validity [155, 156]. Participants will be asked to report daily drug and alcohol use in the specified timeframe (e.g., since the last visit). TLFB will be completed at the following visits: baseline, treatment initiation, and weeks 4, 8, 12, 16, 20, and 24 (or the end of study visit, if not week 24) for assessment of secondary outcomes. Baseline TLFB assesses use in the 30 days prior to informed consent through to the date of the baseline visit.

14.4 Visual Analog Craving Scale (VAS)

Participants’ craving for opioids, alcohol and tobacco will be documented on a visual analog scale (VAS) that ranges from 0 (no craving) to 100 (most intense craving possible). Participants will be instructed specifically to indicate the overall intensity of craving experienced. This scale will be completed at baseline and at 4, 8, 12, 16, 20, and 24 weeks (or the end of study visit, if not week 24) for assessment of secondary outcomes.

14.5 Treatment Services Review (TSR), Version 6 (28 days)

Select items from the Treatment Services Review, Version 6 (TSR-6) addiction treatment modules will be used to collect data on the number of counseling sessions attended in the past 28 days, as well as detoxification, outpatient, inpatient, and medication-assisted addiction treatment services [157]. Participants will complete a modified TSR-6 at baseline, treatment initiation, and 4, 8, 12, 16, 20, and 24 weeks (or the end of study visit, if not week 24) for assessment of TAU and counseling exposure in both TAU and XR-NTX arms.

14.6 Medication-Assisted Treatment

To assess study drug and other medication-assisted treatment exposure, TSR-6 responses will be augmented regarding use of medications for treatment of addiction with additional items asking specifically about use of methadone, buprenorphine, and extended-release naltrexone during the past 28 days for participants randomized to both TAU and XR-NTX arms. Participants will be asked to report the number of days in the past 28 days that each medication was taken at least once per day. This information will be collected from participants at baseline, treatment initiation, and weeks 4, 8, 12, 16, 20, and 24 (or the end of study visit, if not week 24). Additional information gleaned from medical record review to assess the dose and number of days of treatment prescribed for each medication will further augment this assessment.

14.7 Quality of Life

We will measure quality of life using the EuroQol Group 5D (EQ-5D), a validated, self-reported, 5-item instrument used to measure health-related quality of life in a wide variety of populations. The form will be collected at the baseline and week 24 visit. [158, 159]

14.8 Participant Treatment Preference

We will collect each participant's preference for agonist or antagonist treatment using the Participant Treatment Preference form. This form consists of a single item that collects participant treatment preference on a slider scale of 1-10, with 1 being "strongly prefer buprenorphine or methadone (agonist treatment)," 10 being "strongly prefer extended release naltrexone (antagonist treatment)," and 5 being "no preference." The form will be collected via participant self-report at baseline.

15.0 SAFETY ASSESSMENTS

15.1 Adverse Events, including Serious Adverse Events, and Protocol Deviations

Adverse Events, Serious Adverse Events, and Protocol Deviations will be assessed and documented.

Study staff members will assess for any medical or psychiatric side effects by asking: "How have you been feeling since your last visit?" AEs will be solicited at each study visit but will be recorded at any visit after consent when reported by the participant according to the adverse event reporting definitions and procedures outlined in the protocol.

If a reported AE suggests medical or psychological deterioration, it will be brought to the attention of the study clinician for further evaluation. SAEs will be medically managed, reported, and followed in accordance with applicable regulatory requirements. Safety assessments will be performed at all visits.

15.2 Non-Fatal Overdose

Non-fatal opioid overdoses in the past 4 weeks will be assessed using a self-reported instrument used in previous studies at baseline and 24 weeks (or the end of study visit, if not week 24) [160]. Overdose events are sentinel events that are less likely to be prone to recall bias than other events. If non-fatal overdose resulted in a serious adverse event, it should also be captured on the AE/SAE CRF.

15.3 Fatal Overdose

We will collect data on fatal opioid overdoses using medical chart record review at 24 weeks for participants who are lost to follow-up. We will supplement this with information from contacts with persons listed on the participant's locator form when participants are lost to follow-up throughout the study. If a fatal opioid overdose occurred, the event also should be captured on the AE/SAE CRF.

15.4 Precipitated Withdrawal

For participants assigned to XR-NTX, the study clinician will record the presence or absence of precipitated opioid withdrawal on the XR-NTX Administration (INJ) CRF following each XR-NTX injection.

15.5 Concise Health Risk Tracking - Self Report (CHRT-SR) Suicidal Behavior Evaluation

The CHRT-SR [161] is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) [162]. The CHRT-SR will be assessed at screening, treatment initiation, the safety visit, and weeks 4, 8, 12, 16, 20, and 24 (or the end of study visit, if not week 24). The CHRT-SR will assess high risk suicidal ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of, thoughts of how and/or a specific plan to commit suicide) and prompt a clinician assessment for suicide risk before leaving the clinic.

15.6 Concise Health Risk Tracking - Clinician Rated

The Clinician Rated (CHRT-CR) [161] assessment will be performed by the study clinician only if a participant answers any of questions 14-16 on the CHRT-SR as “Agree” or “Strongly Agree” as described in Section 15.5.

15.7 Patient Health Questionnaire (PHQ-9) Depression Symptoms

We measure depression symptoms using the self-reported PHQ-9, a 9-item scale validated for screening, diagnosing, and assessing the severity of depression symptoms in diverse populations [163]. The PHQ-9 will be administered at baseline, 12, and 24 weeks (or the end of study visit, if not week 24). Endorsements of suicidality on the PHQ-9 will be addressed locally at each site.

15.8 Suicidal Risk

This assessment will be performed by research staff if the participant endorses suicidality on the PHQ-9 by answering Q9 (“Thoughts that you would be better off dead, or of hurting yourself in some way”) as “Several days”, “More than half the days” or “Nearly every day.”

16.0 STUDY CONDITIONS

The two study conditions are: 1) office-based XR-NTX, and 2) TAU. Study conditions are discussed in detail in section 4.2, 4.3, and 9.0.

16.1 Clinic-Based XR-NTX

The office-based XR-NTX study condition is discussed in detail in Sections 4.2 and 9.0.

16.2 TAU

The TAU study condition is discussed in detail in Sections 4.3 and 9.0.

16.3 Training

Training in study-specific assessments will be provided as specified in a comprehensive training plan that will be developed by the Lead Team, which includes the Lead Node, CCTN, CCC and DSC staff. The training sessions will include modules targeting all research team members conducted via web, telephone and/or in-person training sessions. Training will cover standard NIDA training for all CTN Trials (e.g., Human Subjects Protection and Good Clinical Practices), as well as protocol specific training as needed (e.g., assessments, study intervention, fidelity to the protocol, safety procedures, data management and collection, research procedures). Attention will be given to provide the study clinic staff providers training in management of opioid and alcohol withdrawal, XR-NTX induction and maintenance, and to familiarize study personnel with study procedures. Support mechanisms are identified (e.g., who to contact for aid, questions, resources) as well as re-training procedures. All study staff will be required to complete any local training requirements per study site and IRBs. Further details are presented in the study Training Plan.

16.4 Concomitant Medications

Participants will be instructed to contact the study clinician at their research site if they plan on taking any concomitant medications (including prescription, over-the-counter, and herbal supplements) during the course of the study. Concomitant medications will also be assessed at screening.

As described in the eligibility criteria, participants will be excluded if there is a need for ongoing opioid analgesic treatment. The study clinician may also exclude any participant taking medications that could interact adversely with study drugs, at his/her clinical discretion.

Study screening and treatment induction procedures (requirement for negative UDS for opioids on day of induction – XR-NTX arm only) are anticipated to greatly decrease the risk of precipitating opioid withdrawal. In the event a participant experiences opioid withdrawal following XR-NTX injection, the study clinician may dispense symptomatic treatments (e.g., oral clonidine, prochlorperazine, ibuprofen, etc.) to alleviate symptoms of opioid withdrawal, according to local SOPs. XR-NTX can also be associated with transient nausea unrelated to opioid withdrawal, typically lasting 2-8 hours. Should participants develop nausea or vomiting during naltrexone induction, this will be treated with oral anti-emetics (e.g., prochlorperazine) as needed.

17.0 STATISTICAL ANALYSIS

17.1 Primary Objective of the Analysis

The Primary objective of the CTN-0067 CHOICES scale-up study is to discover whether HIV clinic-based XR-NTX is non-inferior to TAU with respect to HIV viral suppression in HIV-infected participants with opioid use disorder. We have chosen a non-inferiority margin of 0.75. That is, we will reject the null hypothesis of inferiority of XR-NTX to TAU in favor of non-inferiority if the lower 95% confidence limit for the ratio $\frac{\Pr(suppresed|NTX)}{\Pr(suppressed|TAU)}$ is strictly greater than 0.75. We anticipate a sample size of 350 (175/arm) will grant at least 80% power for the non-inferiority conclusion.

17.2 Primary Outcome Measure

The primary outcome measure for CTN-0067 CHOICES scale-up study is HIV viral suppression. HIV viral suppression is defined as an HIV-1 RNA ≤ 200 copies/ml at 24 weeks from time of randomization.

The binary RMVL model of Rose et al. will be used to predict the log of the risk ratio (not the log of the odds) for suppression via a generalized estimating equation with an exchangeable covariance structure for all the values of a single participant. Baseline alcohol use disorder and sites are included as fixed effects. The fixed effects part of the model is thus:

$$\log(p_{ij}) = \alpha + \beta * trt_i + \gamma * month_j + \theta * trt_i * month_j + \tau * alc_i + \delta_1 * site_{1i} + \cdots + \delta_k * site_{ki}$$

where p_{ij} is the probablility of suppression of participant *i* in month *j*, *trt* is the indicator for treatment, months enter linearly, there is a time by treatment interaction, *alc* is an indicator for baseline alcohol use disorder, and $site_1, \ldots, site_k$ are site indicator variables. The model will incorporate 2 time points for each patient (months 3 and 6), with a contrast used to estimate the treatment effect at month 6. The following SAS fragment shows how to implement this analysis:

```
proc genmod data = visits descending;
class suppressed trt site projid alc base;
model suppressed = trt | month alc site / dist = bin link = log;
repeated subject = projid / type = exch;
estimate "6M trt eff" trt 1 -1 trt * month 6 -6
run;
```

Note that the estimate statements assumes the following coding: trt= (ntx, tau) month = (3, 6).

The RMVL is a type of longitudinal model. In theory, longitudinal models can accommodate missing data better than non-longitudinal models because they incorporate all non-missing data points. But this approach assumes that missing data are not informative, that is, that missing values are probably similar to corresponding non-missing values with the same set of other predictors. For trials of substance-using individuals, missing at random (MAR) is less likely than missing not at random (MNAR) alternative: if data are missing, it is probably because the participant is unsuppressed. So, for the primary analysis, “unsuppressed” will be substituted for missing suppression status values. An exception is that, if missing data are flanked on both sides by “suppressed” values, we will impute the missing data to be suppressed. Since death is at least

as undesirable as lack of suppression, “unsuppressed” will be assigned as a status value for visits subsequent to death. A secondary sensitivity analysis will explore the extent to which trial conclusions need to be changed as the missingness assumption approaches MAR.

17.3 Secondary Outcome Measures

1) Secondary HIV outcomes variables:

a. VACS Index. Change in VACS Index score at 24 weeks compared with randomization (continuous; laboratory assays and demographics).

b. CD4 Count. Change in CD4 count at 24 weeks following treatment initiation compared with randomization (count; laboratory assay).

2) Engagement in HIV Care Variables:

a. ART prescribed. Proportion of participants prescribed ART within 24 weeks following randomization (binary; medical record abstraction).

b. ART Adherence. Proportion of participants taking 100% of prescribed ART doses in the past month at 24 weeks for those prescribed ART at any point during the 24 week trial (binary; self-reported medication adherence measure).

c. Retention in HIV Care: Proportion of participants with at least 1 HIV primary care visit in the past 12 weeks, measured at week 24. Adherence to HIV clinic visits in the year after ART initiation predicts HIV disease progression and death [164] (binary; medical record abstraction).

d. HIV Risk Behaviors. Past 30 day injection drug use, unprotected sex, multiple sexual partners as measured by the RAB at week 24 (binary; self-report).

e. Quality of life. Past 30 day health-related quality of life as measured by EQ-5D at week 24.

3) ART Adherence Mediation Variables:

a. Days of Opioid Use. Number of days of opioid use since baseline, measured by Timeline Followback at 24 weeks (count; self-report).

b. Opioid Abstinence. Past 30 day opioid abstinence (by Addiction Severity Index (ASI)-lite self- report, Time-Line Follow-Back (TLFB) and urine drug screen (UDS) confirmation) in the final 30 days of the 24 week trial (binary; self-report + UDS).

17.4 Sample Size and Duration of Recruitment Phase

The CTN-0067 CHOICES scale-up trial will randomize 350 participants with opioid use disorder who are unsuppressed at baseline from no more than 8 sites over approxmiately 22 months for a power of 80%. Justification for this decision follows.

The trial will be powered as a non-inferiority trial since the overall goal of the research is to add to rather than to supplant the available effective opioid agonist treatment options currently available.

17.5 Substantive Justification for a Non-Inferiority Design.

A non-inferiority trial and the attendant choice of margin must be justified not just statistically, but also on substantive grounds. A non-inferiority trial design is justified when the active control is well-established and effective, and when a non-active control would be unethical, as in the case of treatments for HIV infection [165]. Both conditions are salient to the CTN-0067 CHOICES scale-up study in that opioid agonist therapy with buprenorphine or methadone is considered the standard of care for treatment of opioid dependence in HIV infected patients [104], and placebo treatments for either opioid use disorder or HIV infection are unethical.

Reporting of non-inferiority methods must include [165, 166]:

- Non-inferiority margin (delta)
- Sample size calculation must take into account the margin
- Both ITT and per-protocol analyses must be presented
- Confidence intervals for the results must be presented
- Justification of the margin

The first 4 points have been addressed in other parts of this statistical section. The following section describes the justification for the margin.

17.6 Justification of the Non-Inferiority Margin

Little data exist to inform justification of non-inferiority margins. Given that our primary outcome measure is viral suppression, we reviewed recent non-inferiority trials comparing two antiretroviral regimens with viral suppression as the outcome. Noninferiority margins in these trials ranged from 10% to 15% [114, 167-169], though no published justification is provided for these estimates.

The only study to estimate virologic suppression in HIV-infected participants receiving BUP/NX was the BHIVES collaborative. BHIVES was an observational study of HIV-infected participants with opioid use disorder receiving office-based BUP/NX from their HIV providers. Participants not already on ART baseline were offered ART regimens available in 2004-2007, which were less potent than currently available regimens. Among 64 participants who were not prescribed ART at baseline and who were prescribed BUP/NX for at least 3 quarters, 57.3% achieved HIV viral suppression by 6 months (a timeframe comparable to CHOICES 24-week outcome) [29]. More information about the choice of margin is given in the following section on Power results.

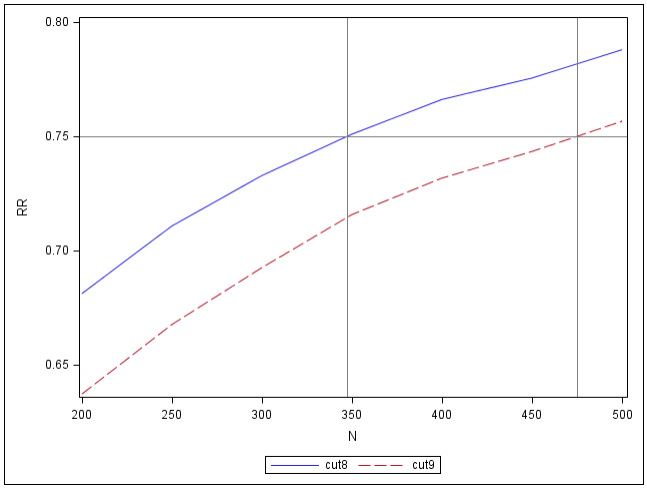
17.7 Rationale for Sample Size

Figure 4 shows the non-inferiority margin required for power of (0.8, 0.9) (using the lower tail of the two-sided 95% confidence interval) as a function of the sample size for the non-inferiority test of XR-NTX versus TAU at 4 months, as estimated from data “random-assignment-bootstrapped” from the (opioid + overlap) group who were unsuppressed at baseline in the pilot study (CTN-0055). There are only 9 participants in the bootstrap population: 7 in Core and 2 in UBC. The random-assignment bootstrap approach was used at 4 months as a conservative way to estimate power in the scale-up (see appendix). The margin is expressed in terms of the risk ratio (RR), that

is, Pr(suppressed | XR-NTX) / Pr(suppressed | TAU)[1]. A horizontal reference line in **Figure 4** marks RR = 0.75, and vertical reference lines mark the intersection of the horizontal line with the power curves for (0.8, 0.9). The vertical lines intersect the N axis at sample sizes of about (350, 480). For a given sample size, use of a margin at or below the one specified by the relevant curved line will grant power in excess of that depicted by the line. For example, an RR margin less than or equal to 0.75 will grant a power of at least 90% for total sample size (both arms together) of about 480, and will grant a power of at least 80% for total sample size of 350. We have chosen this last point upon which to base our sample size.

This particular example is calculated using the Rose et al. binary RMVL model. The fixed effects in the model are treatment, visit number (continuous), time by treatment interaction, baseline alcohol, and site (categorical). The data for each participant are assumed to have an exchangeable correlation structure. Missing data are assumed to be unsuppressed. Note that cases in which the model failed to converge or converged but SAS flagged the result as questionable have been dropped from this analysis. The number of analyzed iterations was (9020, 9492, 9696, 9819, 9848, 9869, and 9911) for n = (200, 250, 300, 350, 400, 450, 500), respectively. With the assumptions above, a non-inferiority sample size calculation was performed using commercial software PASS and got very similar results.

17.7.1 Figure 4. Non-inferiority margins granting power = 0.8 and 0.9 as a function of sample size



Additional Comments Concerning Choice of RR margin

The reasoning in the non-inferiority margin calculation of a RR of 0.75 is as follows:

[1] As we define it here, RR might better be termed a “benefit ratio,” but we shall retain the common usage.

Recall from above that, in BHIVES, 57.3% achieved HIV viral suppression. Let us assume that, in the absence of any treatment for OUD, the suppression rate will be about 15%, so that the treatment effect of the active control in CHOICES is about 42%. It makes intuitive sense that the non-inferiority margin should be some fraction of this, and this general approach is discussed by the FDA in their Guidance for Industry on Non-inferiority Clinical Trials [170]. We have chosen 1/3 as the clinically reasonable fraction. That is, if XR-NTX preserves 2/3 or more of the effect of BUP/NX over placebo, we will consider XR/NTX to be non-inferior to BUP/NX. This implies a margin of 14%. With this margin, we are implicitly saying that, if the true suppression probability for BUP/NX is 57%, then we consider any true XR/NTX suppression probability greater than 43% to indicate that XR/NTX is not inferior to BUP/NX.

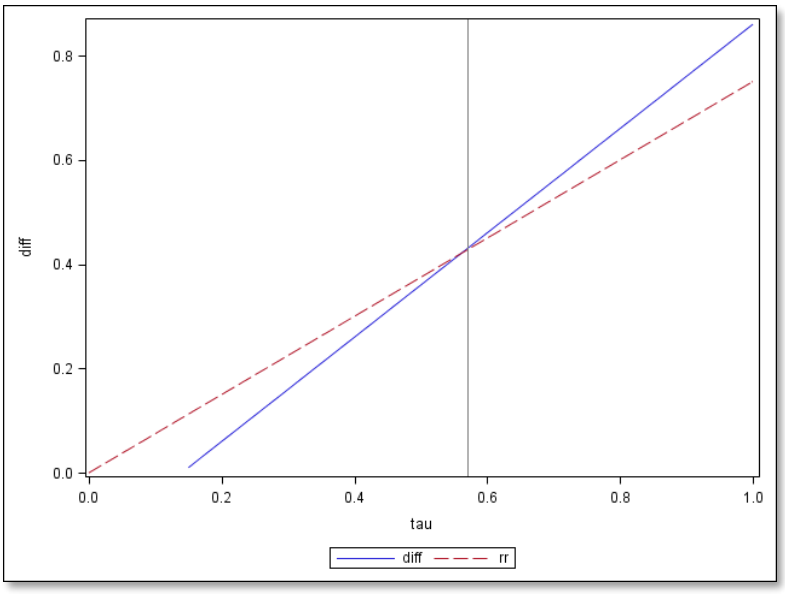
To turn this reasoning into a RR calculation, NTX is non-inferior if the observed risk ratio significantly exceeds 43/57=0.75.

The RR we can be derived from the pilot study data. There are 9 in the opioid + overlap group who started out unsuppressed. Their last non-missing suppression status is as follows:

	TAU	NTX
Suppressed	3	2
Unsuppressed	2	2

The suppression rates from the CTN-0055 pilot study are (TAU, NTX) = (60%, 50%). To call NTX non-inferior, NTX needs to preserve at least 14 percentage points of the TAU suppression rate, which means an NTX suppression rate of at least 60%-14% = 46% is needed. This means a RR of at least 46/60 = 77%. This is not much different from the 43/57 = 75% discussed above. Note that data paucity militates against a more precise calculation of pilot study RR.

17.7.2 Figure 5. Implications for probabilities of fixing RR = 0.75 versus fixing a probability difference of 0.14

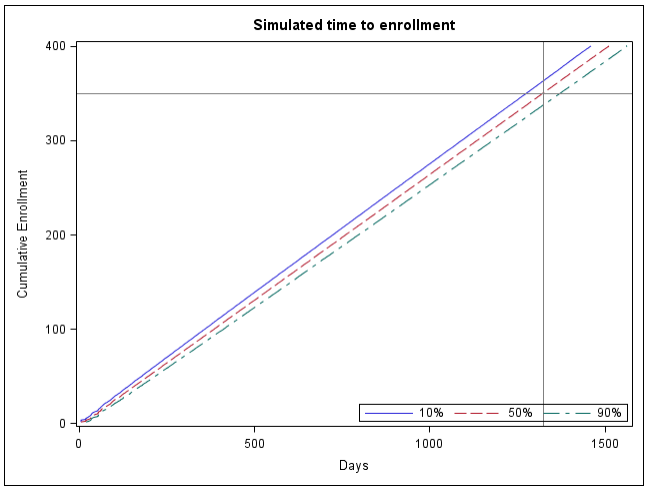


How different are the implications for probabilities if one fixes an RR at 0.75 versus a probability difference of 0.14? **Figure 5** shows, p (suppressed | NTX) as a function of p (suppressed | TAU) for a risk ratio of 0.75 (red dashed line) and a probability difference of 0.14 (blue solid line), with a vertical reference line at p(suppressed | TAU)=0.57, where the two lines intersect. In the neighborhood of p (suppressed | TAU) = 0.57 (from, say 0.4 to 0.8), differences appear to be less than 0.05.

17.8 Duration of Recruitment Period

An enrollment simulation based on CTN-0055 data was run using only times from the study population of interest (opioid + overlap, not suppressed at baseline). Use of the pilot data for estimating duration of recruitment period is limited by the fact that the CTN-0055 CHOICES pilot study sites were encouraged to enroll both participants with OUD and also those with AUD. Enrollment of both groups occurred faster than anticipated, but the opportunity cost of enrolling AUD participants may have limited the observed pace of enrollment of OUD participants. Additionally, no attempt was made in CTN-0055 to enroll only participants with unsuppressed HIV viral loads. Using the pilot study data for only participants with OUD and non-suppressed HIV viral loads, times to recruitment assuming a target sample size of 350, drawn from sites that match the experience of the CTN-0055 sites (one site like UBC and 9 like CORE), are depicted in **Figure 6**. The intersecting reference lines for a sample of size 350 show that simulation suggests a recruitment period of about 1324 days = 44 months. We anticipate that expanding CTN-0067 to include 6-8 sites with a higher prevalence of HIV viral non-suppression among patients with untreated opioid use disorder will allow recruitment of 2 to 3 participants per month per site, thus requiring 22 months to recruit 350 participants.

17.8.1 Figure 6. Simulated times to enrollment of 350 participants from 8 sites like CORE Center.



17.9 Analysis of secondary outcomes

Secondary outcomes will be analyzed as indicated in the italicized text describing each secondary endpoint.

1) Secondary HIV outcomes:

a. **Change in VACS index** at week 24 compared with randomization (score based on lab measurements). T-test.

b. **Change in CD4 count** at 24 weeks following randomization compared with randomization *(count; laboratory* measurement). T-test.

2) Engagement in HIV Care:

a. **ART prescribed** Change in the proportion of study participants prescribed ART within 24 weeks following randomization, compared to baseline (binary; medical record abstraction). *Each individual can be scored either 0 (not prescribed ART) or 1 (prescribed ART) at both baseline and follow-up, after which his or her outcome score will be the follow-up score minus the baseline score. Outcome scores will be analyzed via rank-based methods such as Wilcoxon rank-sum tests. Covariates can be considered via the cumulative logit model.*

b. **ART Adherence** Proportion of participants taking 100% of prescribed ART doses in the past month at 24 weeks for those prescribed ART at any point during the 24 week trial *(proportion; self-reported medication adherence measure). Chi-squared test comparing proportion to treatment assignment, for those prescribed ART*.

c. **Retention in HIV Care** Number of HIV primary care visits at 24 weeks (count, chart abstraction). *Outcome scores will be analyzed via rank-based methods such as Wilcoxon rank-sum tests.*

d. **HIV Risk Behaviors** Past 30 day injection drug use, unprotected sex, multiple sexual partners as measured by the RAB at week 24 (binary; self-report). *Chi-squared test comparing proportion to treatment assignment.*

e. **Quality of life** Past 30 day health-related quality of life as measured by EQ-5D at week 24. *Change from baseline in mean EQ5D score assessed by treatment group using paired t-test, or analysis of change via ordinary least squares.*

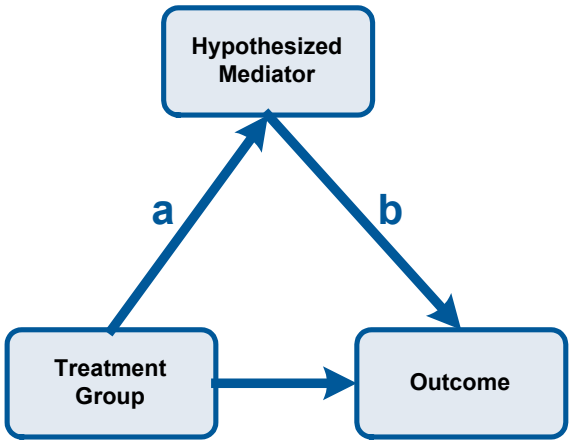
3) ART Adherence Mediation Variables and Mediation Analysis:

a. **Days of Opioid Use** Number of days of opioid use between baseline and 24 weeks, measured by TLFB (count; self-report), will be used to compare opioid use by treatment group. Confirmatory analysis will assess opioid use by the number of days of opioid use in the last 30 days of the study (by ASI-lite; count; self-report) and the number of monthly urine drug screen (UDS) negative for opioids between baseline and 24 weeks *(count; laboratory data). Analyzed using rank-based methods such as Wilcoxon rank-sum tests.*

b. **Opioid Abstinence** Past 30 day opioid abstinence (by Addiction Severity Index (ASI)-lite self-report, Time-Line Follow-Back (TLFB) and urine drug screen (UDS) confirmation) in the final 30 days of the 24 week trial (binary; self-report + UDS).

Analyzed via rank-based methods such as Wilcoxon rank-sum tests. Covariates can be considered via the cumulative logit model.

Mediation Analysis



Mediation will be tested using structural equation modeling with Mplus 7.3. These models estimate the effect of the intervention on the potential mediator (path a, e.g., the effect of intervention on *substance use*) and the effect of the mediator on the outcome or next proximal intermediate outcome (path b, e.g., the effect of *substance use* on *HIV medication adherence*). Longer mediation pathways can also be tested (e.g., a*b*c), and therefore the entire mediational path depicted in section 1.2.1 can be assessed in this framework. There is significant mediation if the product of these two paths (a*b) is greater than zero (or the product of more pathways in a longer mediational chain). Statistical significance will be assessed using bias-corrected bootstrap confidence intervals on the product terms [171]. This test is by far the most powerful test of mediation [172] and can test multiple mediating pathways within a single structural model. Using the tables in Fritz and MacKinnon [171], we should have over 80% power for mediation when the standardized path coefficients (a and b) are .164, which corresponds to approximately 2.7% shared variance between the outcome and predictor variable (e.g., treatment and substance for the a-path in the example given above.) We will also examine whether there are differences in strength of mediational pathways across the opioid and alcohol disorder subgroups.

Qualitative Analysis of Implementation Data The qualitative team creates a coding scheme, practices coding, and revises in an iterative group process. Each transcript is coded and check-coding is completed with 20% of transcripts to ensure inter-coder reliability. The analysis uses a deductive approach to focus on themes related to select CFIR inner and outer setting, provider characteristics, and implementation characteristic domains. Iterative analyses assess convergence of CFIR patient, provider and organizational dimensions on study measures as well as the context of the policy subsystems, cross-system interactions, and resource allocation. A five phase strategy guides the analysis: describe themes, organize and structure data, connect codes and themes, corroborate and triangulate, and condense and summarize findings [173]. Site structural data will be triangulated with staff and patient qualitative interviews to integrate an environmental perspective.

17.9.1 Additional Statistical Tests of the Secondary Outcomes

In addition to the methods described after each secondary outcome, statistical modeling will be done using generalized estimating equations (GEEs) models as employed by Liang and Zeger [174] to allow covariate adjustment in factors such as concomitant alcohol use disorder and severity of opioid and alcohol use disorder. Those secondary outcomes that are binary will be tested with a binomial distribution and logit link as implemented in SAS; whereas those secondary outcomes that involve either continuous or ordinal variables will utilize the appropriate distribution and link function. Note that the exact method of analysis will depend on the realized distribution of the particular outcome in this trial. For example, an expected count data variable may need to be modeled using a zero-inflated Poisson regression rather than a standard Poisson regression if there are too many zero observations to fit the standard Poisson. If there is over-dispersion, a

negative binomial (or zero-inflated negative binomial) regression may be appropriate. For these secondary analyses, the overall Type I error will not be controlled.

17.10 ITT and Per-Protocol Analyses, Missing Data and Dropouts

Analysis will be ITT in the sense that participants will be analyzed as being members of the arm to which they were originally randomized. With one exception, we plan in the primary analysis to recode missing data to “unsuppressed” because, in this setting, this seems more realistic than assuming that missingness is non-informative for suppression. The exception is that, if missing data are flanked on both sides by “suppressed” values, we will impute the missing data to be suppressed. Sensitivity analyses will secondarily explore the implications of this MNAR imputation, and outcomes according to treatment received. Per-protocol sensitivity analyses will compare outcomes among those who initiated at least one dose of XR-NTX compared with those who initiated at least one dose of buprenorphine or methadone.

17.11 Interim Monitoring of Primary Efficacy Endpoint

Interim monitoring will be performed of the primary alternative hypothesis that XR-NTX is non-inferior to TAU at 6 months of follow-up, using a non-inferiority risk ratio of RR = Pr(suppressed|NTX)/Pr(suppressed|TAU) = 0.75. There will be no interim efficacy monitoring before 1/3 the participants have attained 24 weeks of follow-up and a sample size-re-estimation is performed (see the sample size re-estimation section below). Assuming the re-estimation does not call for a change in sample size (which would have to be ratified by the DSMB and approved by NIDA), we will on every subsequent DSMB meeting perform interim efficacy monitoring. All interim monitoring will use an O’Brien-Fleming-type boundary with information fraction equal to the proportion of the target sample size with primary outcome, and alpha = 0.025, one-tailed.

Before recommending early termination, the DSMB will consider:

- Internal consistency of primary and secondary results.
- Internal consistency of primary and secondary results by subgroups defined by baseline characteristics.
- Distribution of baseline prognostic factors among the two groups.
- Consistency of primary and secondary results across sites and among sites enrolling larger numbers of participants.
- Possible bias in assessment of primary and secondary response variables.
- Possible impact of missing data from missed participant visits for assessment of the primary and secondary response variables.
- Possible differences in concomitant interventions or medications.

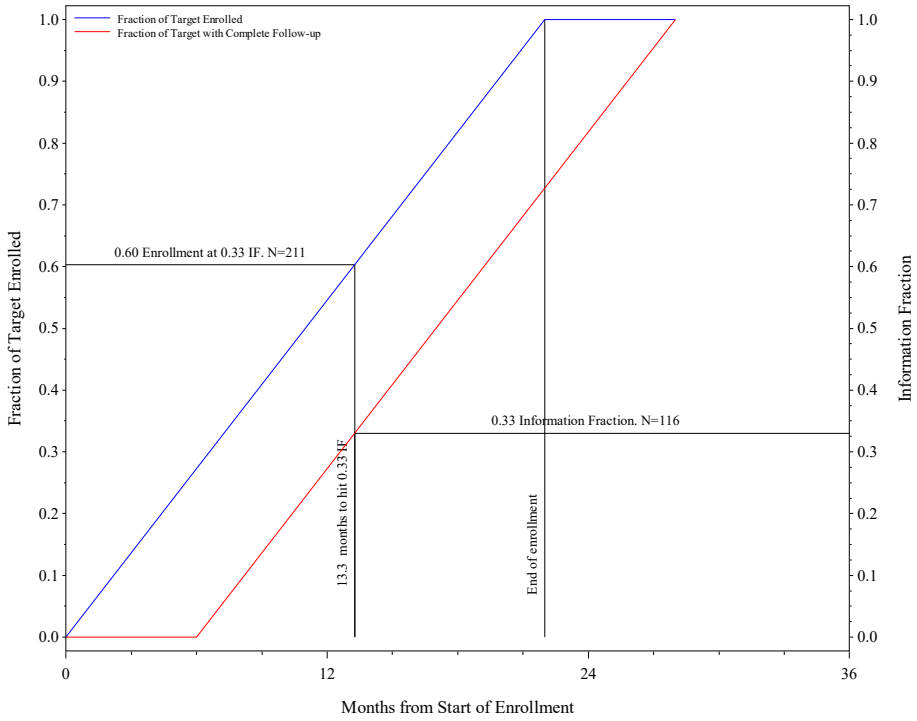
Sample Size Re-estimation

We plan to also perform a sample size re-estimation after about 1/3 off the total expected number of participants (n=116) attain their 24 week outcome, which is approximately 13 months into enrollment. The motivation for sample size re-estimation is that the original sample size calculation was based not only on a hypothesized treatment effect, but also on assumptions about nuisance parameters such as variances and attrition. In the case of CTN-0067, these nuisance parameter estimates are implicitly contained in the Random Assignment Bootstrapping approach we adopted for our sample size calculation, based on pilot data from CTN-0055. It seems reasonable to supplant that calculation with one based on ~100 actual CTN-0067 observations.

The Randomized Assignment part of the Bootstrap approach, when applied to these observations, will automatically suppress the observed treatment effect in favor of one representing the design alternative.

The timing of the sample size re-estimation is based on a number of factors: recruitment rate, timing of primary outcome, and time to perform the sample size re-estimation. For CTN-0067, we use the graphical tool presented in **Figure 7** to assist in assessing the appropriate timing of sample size re-estimation. To illustrate, **Figure 7** shows in a picture the timing of re-estimation when 33% of the participants have outcome data [information fraction = 0.33 (N=116) on the red line] and assuming enrollment (blue line) in CTN-0067 of 350 participants over a 22-month period. This time period to perform the sample size re-estimation corresponds to approximately 13 months after enrollment into CTN-0067 has started, at which point, the study will have enrolled about 60% of the target sample size. If recruitment takes longer or shorter than expected, modifications can be made to the timing of the sample size re-estimation.

17.11.1 Figure 7. Information Fraction and Fraction of Target Enrollment for Proposed Sample Size Re-Estimation Based on Months from Start of Enrollment



17.12 Conditional Power and Futility

Unless otherwise requested, we will perform a futility/conditional power calculation every time we do interim monitoring. If at any DSMB meeting the conditional power falls below 0.3 (when hypothetical future observations are generated under the design alternative RR=1 but tested under the null RR ≤ 0.75), this will stimulate a discussion among the DSMB members about whether we should stop for futility. The conditional power calculation may be carried out via Random Assignment Bootstrapping, similar to the sample-size re-estimation procedure, except that in conditional power, one uses the data already gathered in two ways: first, one includes it in every iteration unchanged as part of the simulated final sample, and second, one Random-

Assignment Bootstraps from it to form the rest of the simulated final sample. In contrast, when one re-estimates the sample size, the entire simulated final sample of each iteration is drawn from the already-gathered sample via Random-Assignment Bootstrapping.

17.13 Safety Analysis

Adverse events (AEs), including serious adverse events (SAEs), will be summarized by body system and preferred term using MedDRA (The Medical Dictionary for Regulatory Activities). Adverse events will be presented in two ways: (1) the number and proportion of participants experiencing at least one incidence of each event will be presented overall and by treatment group; and (2) a table displaying the total number of each event will be given overall and by treatment group. Listings of serious adverse events will be given, sorted by treatment, body system, and preferred term. Detail in these listings will include severity, relationship to study drug, and action taken as available. Treatment arm differences will be monitored by the DSMB.

18.0 REGULATORY COMPLIANCE AND SAFETY

18.1 Regulatory Compliance

This study will use a commercial IRB as the central IRB of record. Sites will be expected to execute an IRB Authorization Agreement between their local IRB and the central IRB. For sites whose IRBs will not rely on the central IRB, procedures will be developed on a case-by-case basis.

Prior to local study initiation, site investigators will obtain written IRB approval (in most cases this will consist of an IRB Authorization Agreement) to conduct the study at their respective sites. When changes to the study protocol become necessary, amendments will be submitted to the central IRB in writing by the investigators for IRB approval prior to implementation. Annual reports will be submitted to local IRBs as required by local guidelines. Each site investigator is responsible for maintaining research files that include copies of IRB-approved consent documents and all IRB/IEC (Institutional Ethics Committee) approval memos for Initial and Continuing/Annual Reviews, protocol modifications, and any other modification made in the course of the study. All initial approval documents (approval memos and informed consents) must be provided to the Lead Node investigative team prior to the initiation of research activities at a given site and all regulatory documents must be available at any time for an audit.

The study will be registered in www.ClinicalTrials.gov.

18.2 Statement of Compliance

This trial will be conducted in compliance with the current version of the protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, informed consent forms, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. This approval is expected to consist of an IRB Authorization Agreement between the local IRB and the central IRB. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved by the central IRB before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures for studies operating under an IRB Authorization Agreement.

18.3 Confidentiality

By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethics Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with that board or committee, affiliated institution and employees. This study will be covered by a federal Certificate of Confidentiality (CoC) protecting participants against disclosure of sensitive information (e.g., drug use). The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating sites will be notified if CoC revision is necessary.

Participant records will be kept confidential by the use of study codes for identifying participants on CRFs, secure and separate storage of any documents that have participant identifiers, and secure computer procedures for entering and transferring electronic data.

18.4 Health Insurance Portability Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. The Lead Node will be responsible for communicating with the IRB and obtaining the appropriate HIPAA approvals or waivers to be in regulatory compliance.

18.5 Investigator Assurances

Each IRB that relies on the central IRB must have on record a Federalwide Assurance (FWA) with the HHS Office of Human Research Protection. This sets forth the commitment of the organization (SITE or IRB) to establish appropriate policies and procedures for the protection of human research subjects, with documentation to be sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA's receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

18.6 Research Advisory Panel of California

Prior to initiating the study, the sponsor or designee will obtain written approval from the Research Advisory Panel of California (RAP-C) if any selected sites are in California. Any planned research project to be conducted in California requiring the use of a Schedule I or Schedule II Controlled Substance as its main study medication as well as research for the treatment of controlled substance addiction or abuse utilizing any drug, scheduled or not must be submitted to RAP-C for review and approval prior to study start-up. Study approval is based on review of the study protocol, consent form, and other pertinent study documents. Yearly reports will be provided to the RAP-C by the sponsor or designee in order to obtain continuing study approval.

18.7 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. It is the responsibility of the investigator and the entire local research team to maintain appropriate disclosure to their individual institution according to their requirements.

18.8 DEA Registration

XR-NTX is not a controlled substance. No DEA registration is required for facilities to receive, prescribe or dispense study drug.

18.9 Drug Accountability

Upon receipt, the investigator, pharmacist, or authorized designee at each site is responsible for taking inventory of the study drug. A record of this inventory must be kept and usage must be documented. Any unused or expired study drug must be accounted for.

18.10 Inclusion of Women and Minorities

Unless specified in the eligibility criteria, the study enrollment is open to any gender, race, or ethnicity. A diverse group of study sites will be involved so that the study can enroll a diverse study population. If difficulties are encountered in recruiting an adequate number of women and/or

minorities, these will be discussed in national conference calls and face-to-face meetings, encouraging such strategies as linkages with medical sites and/or treatment programs that serve a large number of women or minorities or advertising in newspapers or radio stations with a high female or minority audience.

18.11 IND Requirement

Medications to be used in this study will be used in accordance with their approved labeling and therefore there is no plan to submit an IND application.

18.12 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be available at each participating site for inspection and compliance monitoring prior to study initiation, throughout the study, and at study closure.

18.13 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is complete and closed. These records are also to be maintained in compliance with local IRB, state, and federal requirements, whichever is longest. In the case of HIPAA-protected records, this time length is six years. The sponsor and lead investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

18.14 Audits

The sponsor has an obligation to ensure that this trial is conducted according to good research practice guidelines and may perform periodic quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the National Lead Study Team; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors, or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the sites' Institutional Review Board may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

18.15 Reporting to Sponsor

The site principal investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Adverse Event and Serious Adverse Event reporting will occur as described in Appendix A - Adverse Event Reporting Definitions and Procedures. At the completion of the trial, the national Lead Investigator will provide a final report to the Sponsor.

18.16 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. All potential candidates for the study will be given a current IRB-approved copy of the Informed Consent Form

to read. Appropriately qualified and trained study personnel will explain all aspects of the study in lay language and answer all of the study candidate's questions. Participants who remain interested after receiving an explanation of the study will be given an informed consent quiz to test his/her understanding of the trial, the purpose and procedures involved, and the voluntary nature of his/her participation. Those who cannot successfully answer the quiz questions will have the study re-explained by research staff with a focus on those aspects they did not understand. Anyone who cannot demonstrate appropriate understanding of the study will be ineligible to participate and will be assisted in finding other treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the Informed Consent Form. Participants will not be administered any assessments or study procedures prior to signing the informed consent form.

For this study, there will be three consents. There will be two consents for the primary study: one for pre-screening and one for trial consent. The pre-screening consent is verbal only while the trial consent is written and must be signed and dated by the participant. A verbal consent (i.e., waiver of written consent) will also be required for the qualitative interview portion of the study. All consents are to be treated equally in terms of regulatory and protocol requirements (e.g., approved by the IRB before site initiation, etc.).

Study sites may use the template approved by the central IRB. A copy of the IRB-approved consents, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the Lead Node prior to the site initiation visit and with each subsequent consent revision. The Informed Consent Form must be updated or revised whenever important new safety information is available or whenever the protocol is amended in a way that may affect a study participant's participation in the trial. The site must maintain the original and signed Informed Consent Form for each participant in a locked and secure location that is in compliance with IRB and institutional policies. The consent forms must also be accessible for quality assurance review and regulatory compliance. Every study participant should be given a copy of the signed document to keep for their reference. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

18.17 Clinical Monitoring

Monitoring of the study site will be conducted on a regular basis using a combination of NIDA-contracted monitors and node Quality Assurance (QA) staff. Investigators will host periodic visits by both the NIDA-contracted monitors and local QA site managers; the purpose of which is to encourage and assess compliance with GCP requirements and to document the integrity of the trial progress. The national and local monitors will audit the following items, but not exclusively: regulatory documents, case report forms, Informed Consent Forms, and any corresponding source documents for every participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant Informed Consent Forms, protocol adherence, reported safety events and corresponding assessments, study drug accountability, and principal investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA CCTN.

Qualified node personnel will provide site management and monitoring for each site during the trial. This will take place as specified by the local protocol team, node PI, or full Lead Team and

will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node (QA) staff will audit source documentation, including all Informed Consent and HIPAA forms (if applicable). Node QA staff will verify that study procedures are being properly followed and that site staff is trained and able to conduct the protocol appropriately. If the node QA staff's review of study documentation indicates that additional training of study personnel is needed, node QA staff will undertake or arrange for that training. Details of the contract, node QA, and data monitoring are found in the study monitoring plan.

18.18 Study Documentation

Study documentation includes all case report forms, workbooks/worksheets, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence and approved current and previous consent forms and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. The original recording of an observation should be retained as the source document. If the original recording of an observation is the electronic record, that will be considered the source.

19.0 SAFETY MONITORING

19.1 Data and Safety Monitoring Board (DSMB)

This study will utilize the CTN DSMB to oversee ongoing trial progress to assure protection of participants' safety while maintaining that the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, evidence that study procedures should be changed, or if the trial should be halted (for safety, efficacy, or recruitment or performance reasons). This process is intended to assure the IRBs, sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in CTN research trials.

Monitoring will begin with the initial review of the protocol during the study development process and continue throughout the study with meetings at least annually. Recommendations and reports from these reviews will be distributed to the site lead investigator for submission to their IRB.

19.2 Protocol Deviations Reporting and Management

Any departure from procedures or requirements outlined in the protocol will be classified as protocol deviations. A protocol deviation is an action (or inaction) that alone may or may not affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. In some cases, a protocol deviation may compromise participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and is cause for corrective action to resolve the departure and to prevent re-occurrence. Protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The decision about whether a deviation from the protocol will be designated as minor or major will be made by the Clinical Coordinating Center (CCC) in conjunction with the protocol's Lead Investigator(s). The consequences will be specified and participating sites will be informed.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC, and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

Additionally, each site is responsible for reviewing the IRB of record's (and their local IRB's, if applicable) definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities. Sites must also recognize that operating under an IRB Authorization Agreement may not excuse them from reporting Protocol Deviations to their local IRBs. Sites are expected to communicate with their IRB as necessary, according to local guidelines.

19.3 Adverse Events (AEs)

The Lead Investigator may appoint a study clinician (MD, DO, NP or PA) for this study, who will review or provide consultation for each serious adverse event as needed. These reviews will include an assessment of the severity and causality of the event to the study intervention (drug or therapy) or other study procedures. The study clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a centralized Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary for submission to IRBs for

regulatory compliance. The Medical Monitor will determine which safety events require expedited reporting to NIDA, the DSMB, pharmaceutical/distributors, and regulatory authorities. This will include events that are serious, related, and unexpected. The study staff will be trained to monitor for and report Adverse Events and Serious Adverse Events.

19.3.1 Adverse Events

For the purposes of this study, mild (Grade 1) and unrelated Adverse Events will not require reporting in the data system. All adverse events will be tracked on a manual (paper only) Adverse Event Log, regardless of severity, seriousness, relatedness, or expectedness.

19.3.2 Serious Adverse Events

For the purpose of this study, the following events will not be reported as an SAE, but will be recorded on study specific forms in the data system.

1) Detox admissions (documented instead on the DTX form).

2) Admission for labor and delivery (documented instead on the Confirmed Pregnancy and Outcomes form).

3) Admission for elective or pre-planned surgery.

The Lead Node will report all other SAEs on the Serious Adverse Event form in the data system Sites must determine if local IRBs will require annual or other SAE reporting.

19.4 Known Potential Toxicities of Study Drug/Intervention

Refer to the package insert for XR-NTX.

19.5 Known Potential Adverse Events Related to the Underlying Clinical Condition and/or Study Populations

Each of the participating research sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each research site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

As this population will have significant ongoing health and substance use issues, events related to complications of HIV, substance use treatment or admission for substance detoxification will be captured on study-specific forms and not duplicately reported as an adverse or serious adverse event. All hospitalizations for other (non-HIV, non-substance-use related) medical, surgical and psychological reasons and deaths will be reported on AE/SAE forms. These data will still be included in the reports to the DSMB at the regular meetings.

20.0 DATA SAFETY MANAGEMENT AND PROCEDURES

20.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Advantage eClinical, a web- based distributed data entry system, will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

20.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in the Advantage eClinical User's Guide.

20.3 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

20.4 Data Collection

Data will be collected at the study sites either on source documents, which will be entered at the site into eCRFs, or through direct electronic data capture. The eCRFs will be supplied by the DSC. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. Paper CRFs and eCRFs should be completed according to the CRF instruction manual and relevant instructions in the study operations manual. The investigator is responsible for maintaining accurate, complete and up- to-date records, and for ensuring the completion of the eCRFs for each research participant.

20.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into the Advantage eClinical system in accordance with the Advantage eClinical User's Guide. Only authorized individuals shall have access to eCRFs.

20.6 Data Editing

Completed data will be entered into Advantage eClinical. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Site staff will resolve data inconsistencies and errors and enter all corrections and changes into Advantage eClinical.

20.7 Database Lock and Transfer

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and “lock” the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

20.8 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

20.9 Data QA

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

21.0 PROTOCOL SIGNATURE PAGE

SPONSOR – CCTN SCIENTIFIC OFFICER OR DESIGNEE

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 5.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.

- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.

- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.

- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.

- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

22.0 REFERENCES

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3. Korthuis, P.T., et al., *Substance abuse treatment in human immunodeficiency virus: the role of patient-provider discussions.* J Subst Abuse Treat, 2008. **35**(3): p. 294-303.
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23.0 APPENDIX A - Adverse Event Reporting Definitions and Procedures

Each participating site's principal investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

23.1 Definition of Adverse Events and Serious Adverse Events

An **Adverse Event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status or any findings from lab results, x-rays, physical examinations, etc., that are considered clinically significant by the study medical clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered **"serious"** (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study medical clinician or sponsor, it:

1) Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study drug/intervention, must be reported.

2) Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.

3) Requires inpatient hospitalization or prolongation of existing hospitalization.

4) Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Is a congenital abnormality or birth defect.

5) Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

23.1.1 Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the investigator brochure or the package insert or is not listed at the specificity or severity that has been observed. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

23.2 Pregnancy

Any pregnancies that occur while a participant is enrolled in the study will be captured on a pregnancy CRF and not separately reported as an AE or SAE. Women who become pregnant

during the active treatment period will be discontinued from further medication administration, referred for medical care, and the pregnancy followed until an outcome is known.

23.3 Medical and Psychiatric History

A thorough medical and psychiatric history during the screening phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic pre-existing conditions, such as arthritis, which are present prior to clinical trial entry, are not considered to be AEs unless the medical clinician deems that the condition has worsened in intensity and/or frequency during the course of the study.

23.4 Site's Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained study staff will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Study staff will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult with the lead team as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to their IRB, per their IRB's guidelines when operating under an IRB Authorization Agreement.

Site staff is required to enter reportable AEs and SAEs in the Advantage eClinical system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate serious adverse events and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type of records or information necessary to provide a complete and clear picture of the SAE as well as events preceding and following the SAE. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

23.5 Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained medical personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review reportable AEs for seriousness, severity, and causality at least on a weekly basis.

23.6 Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event.

Grade 1	**Mild**	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	**Moderate**	Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required, hospitalization possible.

23.6.1 Guidelines for Determining Causality

The study medical clinician will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction: Is there a reasonable possibility that the study drug/intervention caused the event?

Please note that for the purposes of this protocol, events assessed to be mild (Grade 1) and unrelated, though reportable on the manual adverse event tracking log, are ***not*** reportable in the electronic data capture system.

23.6.2 Site's Role in Monitoring Adverse Events

Local quality assurance monitors (Node QA staff) will visit study sites and review respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan may be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

23.6.3 Sponsor's Role in Safety Management Procedures of AEs/SAEs

A NIDA-assigned Medical Monitor/Safety Monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Medical Monitor, Lead Investigator, and designees. All SAEs will be reviewed by the Medical Monitor/Safety Monitor in Advantage eClinical and, if needed, additional information will be requested. The Medical Monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA-assigned Medical Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the Medical Monitor/Safety Monitor in writing for review by the sponsor and DSMB.

23.7 Regulatory Reporting for an IND study

Not applicable as this study is not being conducted under an IND application.

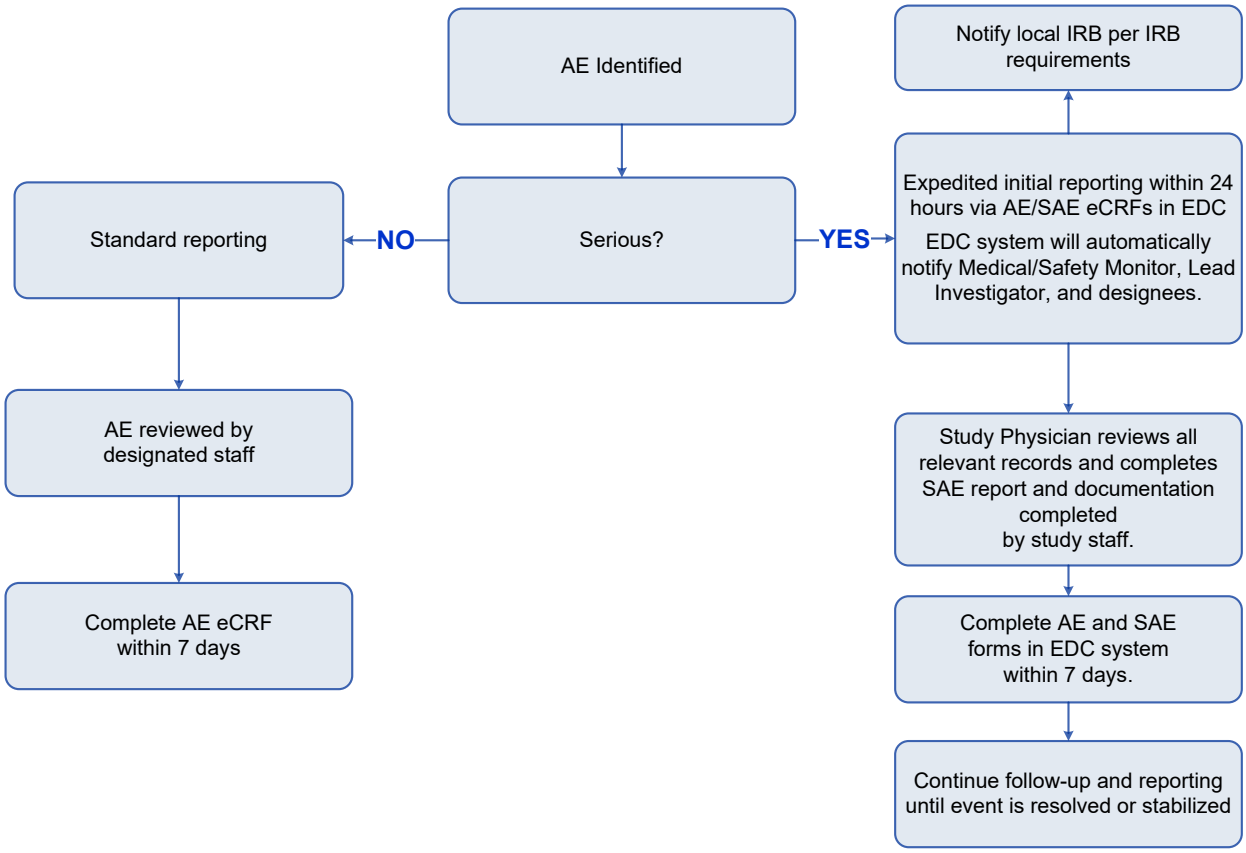
23.8 Reporting to the Data and Safety Monitoring Board

The DSMB will receive a listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

23.9 Participant Withdrawal

The study medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant is withdrawn from further study medication administration. Extended-release naltrexone will be discontinued in participants with evidence of clinically significant deterioration in hepatic function and/or acute hepatitis, as assessed by the study clinician. The study medical clinician should consult with the site principal investigator, the lead investigator and/or Medical Monitor as needed. If necessary, a study medical clinician may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, or the participant has been removed from the study, the participant will be asked to complete an end of study visit to assure safety and to document end of treatment outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.

23.10 Adverse Event Reporting Chart



24.0 APPENDIX B - Data Safety and Monitoring Plan (DSMP)

24.1 Brief Study Overview

The Primary Objective of the CTN-0067 CHOICES scale-up study is to compare the effectiveness of HIV clinic-based XR-NTX in decreasing substance use and increasing HIV viral suppression in HIV-infected participants with opioid use disorder to treatment as usual (TAU) in this population. Details for the definitions and reporting of safety events are found in the protocol (Appendix A).

24.2 Oversight of Clinical Responsibilities

24.2.1 Site Principal Investigator

Each participating site's PI is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Regarding safety, all Adverse Events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the protocol. The assessment of Adverse Events (medical and/or psychiatric) will commence at the time of participant consent and will continue through 30 days post last active treatment visit.

The occurrence of AEs and Serious Adverse Events (SAEs) will be assessed at each clinic visit during the study. Serious adverse events will be followed until resolved or considered stable, with reporting to the CCC Safety Monitor/Medical Monitor through the follow-up period.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events).

24.2.2 Medical Monitor/Safety Monitor

The NIDA Clinical Coordinating Center (CCC) Medical Monitor/Safety Monitor is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed at the time they are reported in the EDC. The Medical Monitor will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed, the Medical Monitor/Safety Monitor will discuss the event with the site. Reviews of SAEs will be conducted in the Advantage eClinical data system and will be a part of the safety database. All AEs are reviewed on a regular basis to observe trends or unusual events.

Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

24.2.3 Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. The DSMB will make recommendations to NIDA as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site)

should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication detailing study safety information will be submitted to participating IRBs.

24.2.4 Quality Assurance (QA) Monitoring

The monitoring of the study site will be conducted on a regular basis using a combination of NIDA CCC contract monitors and the local Node QA monitors. Investigators will host periodic visits for the NIDA CCC contract monitors and Node QA monitors. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. Areas of particular concern will be the review of Inclusion/Exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and Principal Investigator supervision and involvement in the trial. The Monitors will interact with the sites to identify issues and re-train the site as needed to enhance research quality.

QA Site Visit Reports will be prepared by the NIDA CCC contract monitors following each site visit. These reports will be forwarded to the site Principal Investigator, the study Lead Investigator and NIDA.

24.2.5 Management of Risks to Participants

24.2.5.1 Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations.

24.2.5.2 Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required to be reported and the fact that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

24.2.5.3 Human Subject Protection

The study medical clinician will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. Adverse events (AEs) and concomitant medications will be assessed and documented at each clinic visit. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end of study visit to assure safety and to document end of treatment outcomes.

24.2.5.4 Pregnancy

Pregnancy is an exclusion criterion for study participation. A positive pregnancy test post-randomization will result in the cessation of study medication. Participants who discontinue medications will be expected to continue with study visits. Pregnancy test results and related outcome information will be collected on a Pregnancy and Outcome CRF. The site staff will follow the participant until an outcome of the pregnancy is known.

24.2.5.5 Study Specific Risks

XR-NTX blocks the effects of exogenous opioids after administration. After treatment, participants are likely to have reduced tolerance to opioids. Following Vivitrol® treatment, opioid use at the end of a dosing interval or after missing a dose could result in potentially life-threatening opioid intoxication (involving respiratory compromise or arrest, circulatory collapse, etc.) Attempting to overcome the blockade effects of Vivitrol® by administering large amounts of exogenous opioids is associated with potential risk of opioid overdose. Participants in this study will receive an information card that will notify clinicians that they are receiving XR-NTX as part of a research study.

24.3 Data Management Procedures

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture system (Advantage eClinical) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

24.4 Data and Statistics Center Responsibilities

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, and 6) perform data cleaning activities prior to any interim analyses and prior to the final study database lock.

24.5 Data Collection and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical, or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into Advantage eClinical in accordance with the instructions provided during project-specific training and guidelines established by the DSC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

The investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

24.6 Data Monitoring, Cleaning and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into Advantage eClinical. As described above, the CCC will conduct regular visits to sites, during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding local Node, the Lead Investigator, the coordinating centers, and NIDA, to monitor the sites' progress on the study.

24.7 Database Lock and Transfer

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

25.0 APPENDIX C - "Random Assignment Bootstrapping"

CTN-0055 to estimate likely power for CTN-0067

It is harder to calculate power for a repeated-measures or time series approach than it is for an approach that just uses data from a single time point. The reason is that, for the time series approach, the model needs the entire time series, not just the concluding data point. **Table 1** contains a (partial) list of the parameters necessary to generate realistic data for the proposed scale-up study.

25.1 Table 1: Some Parameters Necessary to Simulate Realistic Data for CTN-0067

Design Parameters
total sample size
number and spacing of time points
number of sites
States of Nature
autocorrelation of suppression indicator
monthly probability of death
monthly probability of loss to follow-up
monthly probability of going off treatment, ntx arm
monthly probability of going off treatment, tau arm
probability of initiation on ntx arm
probability of initiation on tau arm
monthly probability of suppression in (ntx, tau)
standard deviation of site effect -- perhaps in (ntx, tau)

Although the first 3 of these are design parameters, thus controlled by the investigators, the remainder are states of nature that need to either be assumed or be estimated (with attendant noise) from a pilot study with 51 participants. This list implicitly embodies various simplifying assumptions that may or may not be true. For example, it could be that the probability of dropout depends on whether the participant is or is not suppressed, whether the participant is alcohol-dependent in addition to opioid-dependent, and even which site the participant comes from.

There is an alternative approach that, while it has its own problems, avoids the necessity of explicitly estimating many parameters from few observations and making implicit simplifying assumptions. Instead, we propose to perform the power calculation by bootstrapping data from the pilot study.

This works because, when calculating power for a non-inferiority design, the conventional approach is to calculate it under the alternative hypothesis that the two treatments are the same.

This is accomplished in the simulation by first pooling the two arms of the pilot (i.e., ignoring the treatment arm), then bootstrapping data from the pool, and finally randomly assigning the bootstrapped observations to the two treatment arms. We call this approach, in which a bootstrap sample is drawn and then treatment is randomly assigned to the bootstrapped observations, "**Random Assignment Bootstrapping**."

As remarked above, the Random Assignment Bootstrap approach has its own limitations. Some arise from the small size of the pilot study. Others have to do with differences in pilot study and scale-up designs. Specifically, the proposed scale-up will have VL visits at months 0, 3, and 6, with the primary suppression outcome being assessed at M6. The pilot study had visits at months 0, 1, 2, 3, and 4, but in this simulation we use only visits 0, 2, and 4 to assess the outcome at M4. The pilot study design is less powerful than the scale-up will be because although it has the same number of visits, they are temporally closer together. Also, if there is an outcome difference between arms in CTN0055, random assignment bootstrapping will probably over-estimate the within-arm variance, leading to a smaller power estimate. For these reasons, scale-up power is expected to exceed the power calculated by Random Assignment Bootstrapping of the pilot study.

The power calculations are performed only for the members of the opiate-only + overlap group who are unsuppressed at baseline. There are only 9 participants in this group, with suppression status values at the various visits as given in Table 2.

25.1.1 Table 2: CTN-0055 Treatment Assignment and Suppression

History at weeks 0, 4, 8, 12, and 16 for the 9 individuals comprising the bootstrap population for the power simulation

treatment assignment	00	04	08	12	16
TAU	No	No	No	No	No
TAU	No	Yes	Yes	Yes	Yes
TAU	No	No	No	No	No
TAU	No	No	No	No	Yes
TAU	No	No	Yes	Yes	Yes
NTX	No	No	No	No	No
NTX	No	No	No	Yes	Yes
NTX	No	Yes	Yes	Yes	Yes
NTX	No	No	No	No	No

Bootstrapping depends for its validity upon the probability that the underlying bootstrap sample is representative of the population. This probability decreases as the size of the bootstrap population decreases. But a similar limitation is true of the other approach: the precision of parameter estimates from the pilot study also decreases as the underlying sample size decreases.

Rose et al.'s [175] continuous method has also been implemented. Although this also can be used to calculate treatment effect in terms of proportions, doing so requires its own bootstrapping. This means that the power simulation would require both inner and outer bootstrap loops, resulting calculation times that are so long that the power simulation would not be practicable.